EXHIBIT 12

UNITED STATES DISTRICT COURT OF NEW JERSEY
CAMDEN DIVISION

****
IN RE: BENICAR (OLMESARTAN)
PRODUCTS LIABILITY LITIGATION MDL No. 2606
****

SUPERIOR COURT OF NEW JERSEY
ATLANTIC COUNTY

****
IN RE: BENICAR (OLMESARTAN) MCL No. 299
MEDOXOMIL) LITIGATION
****

PROTECTED INFORMATION

VIDEOTAPED DEPOSITION OF
JERROLD R. TURNER, MD, PhD

Thursday, February 16th, 2017
9:14 a.m.

Held At:
Campbell Campbell Edwards & Conroy, PC
One Constitution Plaza
Boston, Massachusetts

REPORTED BY:
Maureen O'Connor Pollard, RMR, CLR, CSR

Page 182

You equate a case report to an adverse event report, and vice-versa?
A. No, that's not what we were talking about.
Q. I thought you just said that you saw case reports, which are essentially analogous to adverse event reports.
A. No, I said case reports are reports of adverse events. That's not a MedWatch report. MedWatch reports are also reports of adverse events. But I would hope that there's more detail in a case report, in many cases there is not, in many cases the data provided in the case reports is less, but there's a different process, and they are different items.
Q. Do you have an understanding of the concept of power in a clinical study, in RCT for example?
A. Yes.
Q. Do you have an opinion as to whether or not the ROADMAP Study was adequately powered to study adverse events, adverse effects from olmesartan?
A. I understand the concept of power

Page 183

analysis, but I think those statistical details are outside my area of expertise.
Q. You have no opinion on that question, correct?
A. I have no opinion on that question.
Q. Do you know what Daiichi's position is as to whether or not the ROADMAP Study was adequately powered to study adverse drug effects, including gastrointestinal effects? Do you know what Daiichi's position on that is?
A. No.
Q. If the ROADMAP Study was not adequately powered to study any adverse effects, including gastrointestinal adverse effects, that would be significant, right?
A. Sure.
Q. You don't know the answer to that question, though, right?
A. I don't know the answer to that question. I know it was a pretty huge study.
Q. If the ROADMAP Study was not adequately powered to study adverse effects such as gastrointestinal side effects, then you would not want to rely on the ROADMAP Study to form an

Page 184

opinion one way or another on the question of whether olmesartan is associated with sprue-like enteropathy, correct?
A. Well, I think you could rely on it to say there's insufficient data if you assume that it was underpowered, and that, you know, a qualified statistician has proven that.
Q. When you say "insufficient data," you mean if it's underpowered it's not going to give you reliable information on that question, right?
A. Right.
Q. I think I might have touched on this with you before, but I want to be very explicit. You don't know whether there were any adverse event reports generated by the -- rephrase.
You don't know whether Daiichi generated an adverse event report or reports regarding ROADMAP Study patients in the olmesartan arm reporting gastrointestinal side effects? You haven't seen those, correct?
A. I haven't seen those.
Q. And you don't know if there are any such adverse event reports in existence in which

Page 185

a patient had both a dechallenge and a rechallenge, and based on the rechallenge the company and the investigator both found that the gastrointestinal side effects were definitely related to the use of olmesartan, you don't know if that exists, right?
MR. PARKER: Objection.
A. Are we talking about MedWatch reports and that level?
BY MR. SLATER:
Q. We're talking about a MedWatch report generated by Daiichi based on a study participant in the ROADMAP Study in the olmesartan arm.
A. I don't think MedWatch reports are of the level of proof that you're implying. I don't think they confirm that something was definitely caused by. I do think you have to check caused by or not caused by. And my general understanding is that if someone anywhere in the chain says I think this might have been caused by, then that dominates and you can't undo that in order to prevent hiding of cases.

Page 230

Q. That is something that is accepted to be done in the scientific community, correct?
A. Correct.
Q. If somebody were to criticize the use of Caco-2 cells here and say why would you use colonic cancer cells in a small intestine study, that would not be a reason to reject the findings, correct?
A. When properly done, and that's a huge caveat, but when properly done, Caco-2 cells differentiate much more like small intestines, so it would not be an adequate criticism. But that assumes that you're using your Cacos in a good condition.
Q. In the study, the investigators are studying or trying to determine the microscopic mechanisms for this condition that they're studying, correct?
A. I would object to the term microscopic. Maybe they're trying to determine molecular mechanisms.
Q. Let me rephrase the question.
In this study, the investigators are studying the molecular mechanism for this entity

Page 231

that they're studying, correct?
A. Correct.
Q. And ultimately, what is your understanding of what their conclusion was?
A. It's a crazy conclusion. This is just a terrible study.
MR. SLATER: Move to strike. Doctor, move to strike.
Q. So let's just answer my question, and then you can call Dr. Murray your buddy and tell him it's a crazy study and it's a piece of garbage, I assume you're going to do that after we get done here, but let's just stick with my question.
A. I don't usually try to create arguments with people. I think if Joe and I were talking and I told him it was a crappy study and why, he'd agree with me. I'm trying to find where they say, but they essentially conclude that IL-15 --
Q. Let me stop there.
MR. PARKER: Whoa, whoa, whoa.
MR. SLATER: I move to strike all the colloquy. I just want to get a clean answer.

Page 232

MR. PARKER: No, no, Adam, you've told me repeatedly I cannot interrupt your experts in the middle of an answer. So let the witness finish his answer, then you can follow up with another question.
A. I think what they've essentially shown is that there's some increased fluorescence with their anti-L-15 antibody, and some ill-defined changes of ZO-1 that they're somehow attributing as having something to do with olmesartan and enteropathy.
Q. Did the study show increased levels of IL-15 based on exposure to olmesartan?
A. No.
Q. Did the investigators running the study think that they saw increased levels of IL-15?
A. It looks like they might have, shockingly enough.
MR. SLATER: Move to strike "shockingly enough."
Q. In order to have a biologically plausible mechanism, one does not need to establish the mechanism on the molecular level

Page 233

for this or any other condition, correct?
A. Correct.
Q. As you understand it, what is the understanding among those who believe this entity exists as to what the biologically plausible mechanism is?
A. There really isn't one. They've drawn analogy to celiac disease wherever possible, and have done immunostains that are sort of self-evident from the traditionally hemotoxin and eosin morphology, but they really don't have a plausible biological explanation.
Q. Have you seen statements in the medical literature that indicate that the olmesartan initiates an immune-mediated response that causes cellular changes that leads to inflammation and villous atrophy, and then the symptoms that are seen with this condition?
A. That's one of the things that's been thrown around, yes.
Q. If accurate, that would be a -- if accurate -- let me rephrase it.
If that is accurate, that would be a plausible biological mechanism, correct?

Page 234

A. Sure. If that happened, it would be a plausible biological mechanism, absolutely.
Q. Do you know whether or not anybody at Daiichi proposed doing a similar study to what they saw here with Caco-2 cells, or any other type of study whatsoever, to try to replicate or disprove this study?
A. I think if they proposed that, it would be foolish, and a study like this one would never be worth doing. I don't know what -- I can't tell you what Daiichi did. I'm not involved with Daiichi.
Q. What study would you propose to do to prove or disprove what the molecular mechanism is? If you wanted to prove that, how would you do that study?
MR. PARKER: Objection.
A. I think that's a hard study to do. I think this is definitely the wrong way. If you do this study, you are at face value assuming that Caco-2 cells should respond in the same way as these rare patients.
So let's start with the assumption that rare patients do have something that's

Page 235

induced by olmesartan that is enteropathy. I don't agree that that's been proven, but let's start with that assumption. You're going to assume that this generic epithelial cell that presumably represents the 99.99 percent of patients who don't have any problems with olmesartan is the appropriate model, and then you by your own self just said it triggers immune-mediated responses. Where are the immune cells? There aren't any.
If we want to then get into the data points they have here, this is technically -- I mean if an undergraduate in my lab showed me this, I would tell them what they did wrong and tell them to go try it again. This is just abhorrent technique throughout this study in the Caco-2 parts. And I would tell Joe that to his face.
Q. If you wanted to try to prove or disprove whether olmesartan medoxomil causes sprue-like enteropathy, what would you do to structure a study?
A. All right. If you want to test parts of that hypothesis, okay, let's start there,

Page 236

let's say you believe that this Caco nonsense is true -- is he listening or is he doing something else?
MR. PARKER: Go ahead, go ahead.
A. So let's say you think this is right, the appropriate thing to do would be to get biopsies from people who suffered from, quote, olmesartan-associated enteropathy, and controls. You can grow intestinal epithelial cells from those patients, and now do that assay and ask if there's a selective effect of olmesartan on the people who got sick that you're attributing to olmesartan versus the people who seem to benefit from olmesartan and have no disease. That would be a place to start if you wanted to look at direct epithelial injury, or, you know, or activation of IL-15 production, or anything like that.
BY MR. SLATER:
Q. Do you agree, disagree, or not have an opinion yet based on the state of science that olmesartan medoxomil when exposed to the small intestine causes in some patients villous atrophy?

Page 237

A. I don't think there's sufficient evidence to conclude that it causes.
Q. Is it still an open question?
A. I think it's an open question. It's very hard to prove a negative.
Q. The prevailing understanding in the medical literature is that yes, in some patients the exposure of olmesartan medoxomil leads to villous atrophy in some patients, correct?
MR. PARKER: Objection. Asked and answered.
A. I think the prevailing opinion is that when you're treating patients, if you think this is a possibility, remove olmesartan, if they do better, call it a win. I don't think that's the same as concluding causation in a rigorous manner.
BY MR. SLATER:
Q. What I'm asking you is this. Those scientists and physicians who have been involved in actually treating patients with this condition and studying the condition, there is a consensus among them that in some patients olmesartan medoxomil leads to villous atrophy in

EXHIBIT 13

Olmesartan and Intestinal Adverse Effects in the ROADMAP Study

To the Editor: We read the article by Rubio-Tapia and colleagues[1] with great interest. In this article, the authors describe the occurrence of severe spruelike enteropathy in 22 patients, all of whom received olmesartan (predominantly 40 mg/d) besides other drugs. All patients had long-lasting diarrhea (3-53 months) and weight loss (2.5-50 kg). Many patients also experienced nausea and vomiting (68% of patients), abdominal pain (50%), bloating (41%), and fatigue (68%). Interestingly, these symptoms disappeared after use of olmesartan was stopped. The authors draw the conclusion that olmesartan may directly be involved in spruelike enteropathy. However, our observation in a large group of diabetic patients treated with 40 mg of olmesartan daily does not support this conclusion. We detected no association between treatment with 40 mg of olmesartan once daily and the occurrence of intestinal adverse effects in 2232 patients treated for a median of 3.2 years in the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study.

The largest prospective, randomized, double-blind study with olmesartan is the ROADMAP study.[2,3] In this study, patients with type 2 diabetes were treated with 40 mg of olmesartan (n=2232) or placebo (n=2215) once daily for a median of 3.2 years, and the occurrence of microalbuminuria (interpreted as an early sign of kidney and vascular damage) was the primary end point. We now analyzed the treatment-emergent adverse events (TEAEs) reported by the study physicians. For this analysis, we selected all intestinal illnesses that typically present with diarrhea and selected all symptoms and conditions that were related to abdominal discomfort, such as pain (Table). A total of 78 patients (3.5%) in the olmesartan arm and 94 (4.2%) in the placebo arm had at least 1 episode of diarrhea or diarrhea-associated diseases. We also observed no difference between the groups in the occurrence of any intestinal TEAE. The incidence of abdominal pain or related symptoms was also comparable (Table). In the olmesartan group, 127 patients (5.7%) experienced at least 1 episode of abdominal discomfort vs 125 (5.6%) in the placebo group. The reported incidences of fatigue and weight decrease were also similar. Furthermore, we determined whether more patients prematurely terminated study participation because of intestinal or abdominal discomfort–related TEAEs. Three patients in the olmesartan group (all 3 having diarrhea) and 3 patients in the placebo group (2 having diarrhea and 1 having gastroenteritis) stopped taking the study medication because of specific gastrointestinal findings. Eight additional patients in each of the 2 study arms stopped taking the study medication because of abdominal discomfort–associated TEAEs not specifically linked to the gastrointestinal tract.

TABLE. Gastrointestinal TEAEs Reported in the ROADMAP Database

Event	No. (%) of patients: Olmesartan, 40 mg (n=2232)	Placebo (n=2215)	*P* value
Intestinal-associated TEAE	78 (3.5)	94 (4.2)	.20
Diarrhea	51 (2.3)	52 (2.3)	
Gastroenteritis	17 (0.8)	25 (1.1)	
Colitis	1	6 (0.3)	
Enteritis	2 (0.1)	4 (0.2)	
Gastroduodenitis	4 (0.1)	2 (0.1)	
Colitis, ulcerative	2 (0.1)	2 (0.1)	
Duodenitis	2 (0.1)	2 (0.1)	
Gastrointestinal disorder	3 (0.1)	1	
Gastrointestinal infection	1	3 (0.1)	
Enteritis, infectious	0	2 (0.1)	
Abdominal discomfort–associated TEAE	127 (5.7)	125 (5.6)	.95
Abdominal pain	61 (2.7)	52 (2.3)	
Upper	26 (1.2)	24 (1.1)	
Lower	2 (0.1)	1	
Location not reported by physician	33 (1.4)	27 (1.2)	
Dyspepsia	34 (1.5)	29 (1.3)	
Nausea	30 (1.3)	34 (1.5)	
Vomiting	13 (0.6)	13 (0.6)	
Flatulence	6 (0.3)	9 (0.4)	
Abdominal discomfort	4 (0.2)	4 (0.2)	
Irritable bowel syndrome	2 (0.1)	3 (0.1)	
Epigastric discomfort	2 (0.1)	2 (0.1)	
Gastrointestinal pain	1	0	
Fatigue	25 (1.1)	20 (0.9)	
Weight decrease	17 (0.8)	11 (0.5)	

ROADMAP = Randomised Olmesartan and Diabetes Microalbuminuria Prevention; TEAE = treatment-emergent adverse event.

In summary, in more than 2200 patients taking high-dose olmesartan for more than 3 years, we did not observe an intestinal effect of olmesartan. In the ROADMAP study, we could not find a link between the occurrence of diarrhea-associated complications and the intake of 40 mg/d of olmesartan. This finding might be because spruelike enteropathy is a rare event. Indeed, the 22 reported cases in the report by Rubio-Tapia et al came from 16 different states and were diagnosed at the Mayo Clinic during a time frame of 3 years. We cannot rule out the possibility

that in this very rare disease the intestinal renin-angiotensin system plays a role; however, our data from the ROADMAP database did not identify a link between olmesartan use and the occurrence of gastrointestinal disease.

Jan Menne, MD
Hermann Haller, MD
Medical School Hannover
Hannover, Germany

Potential Competing Interests: Both authors have received honoraria for lectures from Daiichi-Sankyo. Dr Haller is a medical advisor to Daiichi-Sankyo and was supported by research grants.

1. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc.* 2012;87(8):732-738.
2. Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med.* 2011;364(10):907-917.
3. Haller H, Viberti GC, Mimran A, et al. Preventing microalbuminuria in patients with diabetes: rationale and design of the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study. *J Hypertens.* 2006;24(2):403-408.

http://dx.doi.org/10.1016/j.mayocp.2012.10.005

Small Bowel Histopathologic Findings Suggestive of Celiac Disease in an Asymptomatic Patient Receiving Olmesartan

To the Editor: Rubio-Tapia et al[1] recently reported a possible association of olmesartan therapy with an unexplained severe enteropathy symptomatically resembling celiac disease (CD) or sprue. The 22 patients described were seen at Mayo Clinic in the relatively short period of August 1, 2008, to August 1, 2011. The usual presentation was chronic diarrhea and weight loss, sometimes requiring hospitalization. Onset of symptoms was months to years after initiation of olmesartan treatment. Intestinal biopsy specimens from 15 patients revealed villous atrophy and variable degrees of mucosal inflammation. Five patients had evidence of colonic inflammation. Most remarkably, a gluten-free diet did not resolve symptoms, whereas both marked symptomatic improvement and resolution of histopathologic findings occurred on withdrawal of olmesartan therapy.

We describe a patient who had been taking olmesartan for 3 years at which time small bowel histopathologic findings suggesting CD were documented, but symptoms of CD enteropathy were absent. This anecdotal observation suggests the possibility that olmesartan could be associated with histopathologic findings for a substantial period before the onset of enteropathy or alternatively that such histopathologic findings might persist for years without the onset of symptoms.

A 59-year-old man experienced mild, normochromic, normocytic anemia in 2007. Workup revealed an isolated vitamin B_{12} deficiency (172 pg/mL), which was ascribed to long-term ranitidine therapy for gastroesophageal reflux and which responded to oral vitamin B_{12} supplementation at 1000 μg/d. However, the anemia did not improve. The gastrin level was 41 pg/mL (reference range, <100 pg/mL); the intrinsic factor antibody test result was negative.

Coincidentally, the patient underwent upper gastrointestinal endoscopy for symptoms consistent with worsening gastric reflux. The only macroscopic finding was nodularity in the duodenal bulb consistent with prominent Brunner glands, which was attributed to acid wash. However, a biopsy specimen from the second portion of the duodenum revealed mild expansion of the lamina propria and increased intraepithelial lymphocytes (IELs) with no significant villous blunting, suggesting (but not diagnostic of) possible CD. The patient reported no diarrhea but had occasional mild constipation. He had a first-degree cousin with CD, but no other family members were known to have CD. Findings from a workup for CD were unremarkable, including negative tissue transglutaminase antibody results (0.9 AU; reference range, <7.0 AU), normal total IgA level (127 mg/dL; reference range, 50–500 mg/dL), normal vitamin K_1 level (1.16 ng/mL; reference range, 0.10-2.10), normal prothrombin time, and negative *Helicobacter pylori* antibody results. He was HLA-DQ2 positive but HLA-DQ8 negative.

Because the findings were unusual, a repeated upper endoscopy and a colonoscopy were performed in August 2010. The small bowel gross appearance was unchanged; the colonic examination findings were unremarkable. A small bowel biopsy specimen revealed increased IELs with mild villous blunting (interpreted as unchanged from the prior study); the colonic biopsy results were normal. The tissue transglutaminase antibody test result was again negative, and the total IgA level was normal.

A stool specimen for *Giardia* and *Cryptosporidium* immunoassays, obtained because of an episode of prolonged (6 weeks' duration) diarrhea during international travel 10 years previously, produced negative results. A trial of a gluten-free diet was considered, but the patient elected not to pursue this given the absence of symptoms, the uncertain diagnosis, and the logistical difficulties of dietary adherence during frequent domestic and international travel.

Hypertension had been diagnosed in 2003, and therapy with losartan was initiated. In 2004, losartan therapy was discontinued, and olmesartan therapy, 20 mg/d, was begun. Olmesartan therapy was well tolerated, and the hypertension was well controlled. On publication of the article by Rubio-Tapia et al, olmesartan was identified as a possible cause of the unusual findings. Olmesartan therapy will be discontinued, with monitoring of vitamin B_{12} levels and consideration for repeated upper gastrointestinal endoscopy.

Although Rubio-Tapia et al are careful to avoid claiming a proven causal relationship between olmesartan therapy and the observed spruelike enteropathy, the data are highly suggestive of more than just a coincidental association. The authors posit that the long interval between initiation of olmesartan therapy and onset of symptoms of enteropathy, as observed in their patients, could be consistent with cell-mediated immunity damage. They further suggest that a potential mechanism for the enteropathy could relate to inhibitory effects of angiotensin II receptor antagonists on transforming growth factor β action because transforming growth factor β is important in gut immune homeostasis.

Another interesting observation by the authors is that 68% of their patients

EXHIBIT 14

IN THE UNITED STATES DISTRICT COURT LAW FOR THE DISTRICT OF NEW JERSEY

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IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION : MDL NO. 2606

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THURSDAY, MAY 26, 2016

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PROTECTED INFORMATION

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Videotaped deposition of Donald Hinman, held at the offices of Premier Business Centers, 1003 Bishop Street, Suite 2700, Honolulu, Hawaii, commencing at 9:08 a.m., on the above date, before Carrie A. Campbell, Registered Merit Reporter and Certified Realtime Reporter.

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GOLKOW TECHNOLOGIES, INC.
877.370.3377 ph | 917.591.5672 fax
deps@golkow.com

Page 142

form.
THE WITNESS: Those -- there are SOPs and regulations about the maintenance of the document. I don't know what the procedure is.
QUESTIONS BY MR. SLATER:
Q. To the extent that your company had pathology specimens that were created during the course of the preclinical or clinical trials for that matter that were done as part of the development of the drugs, where would I look to get those?
Where I would want to -- where I would go to find those?
A. I don't know where they're stored.
Q. Okay. As far as you know, those should be preserved and not destroyed; is that true?
A. There are, again, guidelines and SOPs about retention. I don't know what the specifics are.
Q. Based on your general understanding, pathology specimens that were

Page 143

developed as part of the development process, I understand you don't have the SOPs in front of you, but is it your understanding that your company is supposed to preserve those and not discard or destroy those actual type of test specimens?
MR. URBANCZYK: Object to the form.
THE WITNESS: The specimens would be -- I assume were stored according to GLP, and there are specific requirements about that, but I don't have the specifics.
QUESTIONS BY MR. SLATER:
Q. Okay. We saw in some of the e-mails that we went through a request that certain people look at some preclinical pathology.
Remember we saw that?
A. Yes.
Q. If one of those scientists -- rephrase.
If one of the scientists at your company actually did go back and look at

Page 144

preclinical pathology, should that be documented somewhere other than just in an e-mail as part of an e-mail chain?
A. I don't know --
MR. URBANCZYK: Object to the form.
THE WITNESS: I don't know the standard procedure in the labs.
(Hinman Exhibits 458 and 459 marked for identification.)
QUESTIONS BY MR. SLATER:
Q. I just gave you 458, correct?
A. Yes.
Q. This is 459.
Start with those two.
Exhibit 458 is some e-mails written July of 2012.
Do you see that?
A. Yes.
Q. The one at the very top of the first page is an e-mail from someone named Lydia Worms, and she writes to some people and says, "May I ask you to circulate this very important draft letter from Professor

Page 145

Haller, the chairman ROADMAP steering committee, to the" -- I'm going to wait until the siren goes by.
Start over.
At the top of Exhibit 458 is a July 12, 2012 e-mail from someone named Lydia Worms to various people. The subject, urgent, ROADMAP treatment emerge adverse events, and it shows there's an attachment letter HH draft, 11 July 2012.
Do you see that?
A. Yes.
Q. And this person, Lydia Worms, writes the e-mail to a few people and says, "May I ask you to circulate this very important draft letter from Professor Haller, the chairman roadmap steering committee, to the editor of the Mayo Clinic Proceedings with your relevant groups for information and for a fast feedback on any wrongful medically data-related content. Please respond by Friday, July 13th, lunchtime, to Heiko or myself."
Do you see that?

Page 146

A. Yes.
Q. Rephrase.
Now look at Exhibit 459, please. There's an e-mail from Mizue Suzuki to a whole bunch of people, including yourself, July 13, 2012?
Do you see that?
A. Yes.
Q. And the e-mail has the same -- rephrase.
The e-mail subject olmesartan sprue draft action plan, and then it says urgent, ROADMAP treatment emergent adverse events letter HH draft July 11, 2012.
Do you see that?
A. Yes.
Q. And the subject of urgent ROADMAP treatment emergent adverse events and the attachment are the same as that first e-mail I showed you, Exhibit 458.
Do you see that?
A. Yes.
Q. And this e-mail from -- rephrase.

Page 147

This e-mail states, "Dear all, Mizuno-san kindly forwarded me the attachment information. I hope at least regulatory affairs and pharmacovigilance had a chance to review this information."
Do you see that?
A. Yes.
(Hinman Exhibit 460 marked for identification.)
QUESTIONS BY MR. SLATER:
Q. I'm now handing you Exhibit 460, 4-6-0.
And I'll represent to you and we confirmed this with the metadata, this is the attachment to Exhibit 458 and 459, the letter HH draft. The letter -- draft letter from Professor Haller.
Do you see that?
A. Yes.
Q. And this is a draft of a letter proposed to be written to the Mayo Clinic Proceedings journal. We went through that just a moment ago, right?
A. Okay. Yes.

Page 148

Q. Now, you've published in the peer-reviewed literature, correct?
A. Yes.
Q. Okay. A letter to the editor at a journal does not qualify as a peer-reviewed medical journal article, does it, as a general proposition?
A. Well, that's a question for the journals. Not me.
Q. You understand what peer review is, right?
A. Yes.
Q. Just very briefly, what is that, what's your understanding?
A. Peer review means that when an article is submitted to a professional journal, it is distributed to reviewers who -- to other reviewers for review and evaluation before it's -- before review and evaluation.
Q. And at times am I correct as part of the peer review process the article may be sent back to the authors with questions or areas that the journal wants

Page 149

addressed before they'll accept it for publication?
A. Yes.
Q. And sometimes an article may be rewritten multiple times as part of the peer review process before it's actually accepted?
A. Yes.
Q. One of the things that is done in medical journal articles or scientific journal articles is disclosures of potential conflicts of interest, correct?
A. Yes.
Q. And one of the reasons that's done is to disclose areas of bias so people who are reading the articles will understand if there were potential biases that could impact the information communicated, correct?
MR. URBANCZYK: Object to the form.
THE WITNESS: Again, it depends on the editorial policy of the individual journal, yes.
QUESTIONS BY MR. SLATER:
Q. For example, if the authors are

Page 154

can weigh those in when evaluating the information, correct?
A. Yes.
MR. URBANCZYK: Asked and answered.
QUESTIONS BY MR. SLATER:
Q. Now, let's look at Exhibit 460. You see this is a draft of the article that is referenced in Exhibit 458, which was then forwarded to you with Exhibit 459.
Do you see that?
A. Yes.
Q. And it refers to the Rubio-Tapia Mayo Clinic article published regarding the occurrence of severe sprue-like enteropathy in 22 patients of whom all received olmesartan.
That's what it says in the first sentence or two, correct?
A. Yes.
Q. And based on the e-mails I've shown you, this draft was circulated within your company to give comments before it was going to be submitted; that's what the e-mail

Page 155

talked about, correct?
A. Yes.
Q. First of all, did you give any input into the article at all?
A. No.
(Hinman Exhibit 461 marked for identification.)
QUESTIONS BY MR. SLATER:
Q. I've marked as Exhibit 461 the published letter to the editor by Professor Haller and Menne, M-a-n-e {sic}, and if you impair, you'll see this is the published version of what was circulated in draft form in your company. It's not exact, but you see it's the same article.
You can take a quick look and satisfy yourself.
A. This is difficult to determine from just a superficial look whether these are the same, but they appear to be.
Q. Well, you --
A. They're similar.
Q. Well, take more than a superficial look because I'm not going to

Page 156

continue with a qualifier like that; difficult to determine from a superficial look.
Here's my question: If you compare Exhibit 460 with Exhibit 461, does it appear that Exhibit 461 is the published form of the draft that was circulated within your company?
A. Well, it appears that the first paragraph and the last paragraph of the draft and the final are very similar. There are some differences in the middle section.
Q. There are some differences, but does it appear that Exhibit 460 is the -- is a draft of what was ultimately submitted?
A. Could be a draft, yes.
Q. First of all, looking to the end of the letter that was published, Exhibit 461, look just after the two names of the authors, Dr. Menne and Dr. Haller. There's a potential competing interest section.
Do you see that?
A. Yes.

Page 157

Q. And what's your understanding of what that means, potential competing interests?
A. I guess what we've been talking about, disclosure of financial inter -- disclosure of potential conflicts of interest.
Q. They disclose here that both authors -- rephrase.
They disclose here that both authors have received honoraria for lectures from Daiichi-Sankyo.
Honoraria is payment, correct?
A. Yes.
Q. Dr. Haller is a medical advisor to Daiichi-Sankyo, in that capacity, he would be paid, correct?
Ordinarily your medical advisors get paid for that role, correct?
A. I don't know that for a fact.
Q. Dr. Haller is a medical -- rephrase.
It says Dr. Haller is a medical advisor to Daiichi-Sankyo and was supported

Page 158

by research grants.
Research grants are payments to fund studies, correct?
A. Yes.
Q. Is there any disclosure here that you see that a draft of this article was circulated within Daiichi-Sankyo, the manufacturer of the drug being discussed?
Do you see any disclosure of that here?
A. No.
Q. Look, if you could, at the prior page, the front page of the letter to the editor, there's a long paragraph that starts at the very beginning and ends in the second column.
Do you see that?
A. Yes.
Q. Halfway down the second column is a sentence that states, "We detected no association between treatment with 40 milligrams of olmesartan once daily and the occurrence of intestinal adverse effects in 2,232 patients treated for a median of

Page 159

3.2 years in the randomized olmesartan and diabetes microalbuminuria prevention ROADMAP study."
Do you see that?
A. Yes.
Q. Do you see that language in the draft that was sent by Dr. Haller to your company to review?
A. I do not see the same text.
Q. If someone from your company added or requested the addition of language indicating that they did not detect -- rephrase.
If someone from your company added this language or requested the addition or suggested the addition of this language indicating that there was no association between olmesartan and intestinal adverse effects, that would be a material addition to the article, correct?
MR. URBANCZYK: Object to the form.
THE WITNESS: I can't -- I can't make that evaluation.

Page 160

QUESTIONS BY MR. SLATER:
Q. There is no disclosure that the draft -- rephrase.
Do you understand what that means to say that there was no association -- association detected between treatment with olmesartan and the occurrence of intestinal adverse effects?
Do you know what that means?
I'll withdraw it. Save us time.
Can you look in the exhibits, there's an Exhibit 366, please?
It should be in that pile.
A. 366?
Q. Yes.
Before we get to that actually, let's go back to the prior documents. I want to ask you a different question. I apologize.
Looking at the letter that was -- the draft letter that was sent around in your company and then ultimately published as a letter to the editor.

Page 161

Do you see that?
Once your company got that draft letter, if your company saw that there was -- if your company saw that there was any significant information relevant to whether or not olmesartan is associated with sprue-like enteropathy, would the right thing to do have been for your -- the people in your company that saw it to say that the author, "Hey, you know, there's other information that we have that should know and include here to give a balanced statement about our drug?"
MR. URBANCZYK: Object to the form.
QUESTIONS BY MR. SLATER:
Q. Would that have been the right thing to do?
MR. URBANCZYK: Object to the form.
THE WITNESS: That's a question of ethics, and I don't think that I'm prepared to answer that.

EXHIBIT 15

MAYO CLINIC

ORIGINAL ARTICLE

Olmesartan, Other Antihypertensives, and Chronic Diarrhea Among Patients Undergoing Endoscopic Procedures: A Case-Control Study

Ruby Greywoode, MD; Eric D. Braunstein, MD; Carolina Arguelles-Grande, MD; Peter H.R. Green, MD; and Benjamin Lebwohl, MD, MS

Abstract

Objective: To investigate a recent association between the use of the angiotensin receptor-blocker (ARB) olmesartan and a severe enteropathy resembling celiac disease.

Patients and Methods: We searched our endoscopy database for all outpatient esophagogastroduodenoscopy (EGD) or colonoscopy examinations in patients aged at least 50 years during the period January 1, 2007, to March 31, 2013. Cases were those whose examination indication was diarrhea, and controls were those whose examination indication was esophageal reflux (EGD) or colorectal cancer screening (colonoscopy). We compared cases with controls with regard to the proportion of those listing olmesartan among their medications. Secondary exposures were the proportion of those taking non-olmesartan ARBs or other antihypertensive medications. We also examined biopsy results to determine whether there were histologic changes associated with the use of olmesartan.

Results: We identified 2088 patients undergoing EGD and 12,428 patients undergoing colonoscopy meeting inclusion criteria. On multivariate analysis, there was no statistically significant association between olmesartan and diarrhea among those undergoing EGD (odds ratio, 1.99; 95% CI, 0.79-5.00) or colonoscopy (odds ratio, 0.63; 95% CI, 0.23-1.74). Review of pathology reports of the EGD and colonoscopy groups showed no association between the use of olmesartan and the histologic diagnosis of celiac disease (P=.61) or microscopic colitis (P=1.0), respectively.

Conclusion: Our findings suggest that neither olmesartan nor other ARBs were associated with diarrhea among patients undergoing endoscopy. The spruelike enteropathy recently associated with olmesartan is likely a rare adverse effect and milder presentations are unlikely.

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A number of recent reports in the literature have implicated olmesartan, an angiotensin II receptor-blocker (ARB) commonly prescribed for the treatment of hypertension, in the development of a severe form of chronic diarrhea and intestinal villous atrophy resembling celiac disease.[1-3] In an initial case series, 22 individuals were diagnosed with refractory celiac disease because of chronic diarrhea and villous atrophy on histology, although all lacked the diagnostic markers of celiac disease and derived no clinical improvement from a gluten-free diet.[1] These individuals were observed to be taking olmesartan and experienced significant clinical and histological improvement with the cessation of the drug, suggesting a strong association between olmesartan and the development of a severe form of spruelike enteropathy.

A recent review of individuals with villous atrophy of unclear etiology also observed that a number of those originally considered to have unclassified sprue (negative celiac disease serologies despite evidence of villous atrophy on duodenal biopsy) were taking olmesartan.[4] As in the previous study, all these patients had symptomatic improvement after the discontinuation of the drug. Similarly, a case series of patients with collagenous sprue at the Mayo Clinic reported that of 30 patients with collagenous sprue, 27% had been taking olmesartan.[5] Although the diagnosis of celiac disease is made on duodenal biopsy, the finding of microscopic colitis (lymphocytic and/or collagenous colitis) in the large intestine is associated with a diagnosis of celiac disease. Thus, a positive association between microscopic colitis and the use of olmesartan could suggest a

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spectrum of histologic changes associated with the drug. In addition, lymphocytic colitis was present in 22% of the initial case series describing olmesartan-associated spruelike enteropathy.[1]

Another recent case report described similar findings of negative serologic markers despite mild villous atrophy in a patient taking olmesartan; however, unlike the previous reports, this patient exhibited no symptoms of diarrhea, suggesting that olmesartan may produce a spectrum of disease with preclinical or asymptomatic histologic changes.[6]

It is unclear whether these cases described in the literature highlight a very rare reaction to olmesartan, or whether patients with severe disease represent the most clinically overt sample, with milder forms of olmesartan enteropathy left undetected. It is also unclear whether olmesartan alone is associated with this phenomenon or whether other members of its drug class share similar effects. We therefore performed a case-control study with the aim of investigating a possible association between diarrhea and the use of olmesartan among patients undergoing endoscopic procedures. As a secondary aim, we measured for associations between diarrhea and other antihypertensive medication exposures.

METHODS

Patients

Using an electronic endoscopy database, we identified all outpatient esophagogastroduodenoscopy (EGD) or colonoscopy examinations in patients aged at least 50 years during the 75-month period spanning the dates January 1, 2007, and March 31, 2013, at Columbia University Medical Center, a hospital-based endoscopy suite in New York City. As part of routine preendoscopy protocol, all patients were interviewed in person by a nurse and asked to provide a list of all their current medications (prescription as well as nonprescription). Cases were defined as those whose examination indication was listed as diarrhea, and controls were defined as those whose examination indication was esophageal reflux (in those undergoing EGD) or colorectal cancer screening (in those undergoing colonoscopy). We compared cases with controls with regard to the proportion of those who listed olmesartan among their medications. Secondary exposures were the proportion of those taking nonolmesartan ARBs or other antihypertensive medications. We used multivariate logistic regression, adjusting for age and sex, to quantify the association between these drug exposures and case status, that is, diarrhea.

To determine whether there were histologic changes associated with the use of olmesartan, we examined the biopsy results of both the EGD and the colonoscopy groups. We examined the upper endoscopy cases (ie, patients who presented for EGD because of diarrhea) to determine whether there were any diagnoses of celiac disease and whether there was an increased proportion of olmesartan use among those who underwent small intestinal biopsy during the procedure. To do so, we identified patients with celiac disease (either newly diagnosed or previously diagnosed) in this data set using a query for the *International Classification of Diseases, Ninth Revision* code for celiac disease (579.0) followed by manual review of the chart of each case with this diagnosis code. Using the search terms "microscopic colitis" or "lymphocytic colitis" or "collagenous colitis," we also manually reviewed the biopsy reports of colonoscopy cases (ie, patients who underwent colonoscopy because of diarrhea) to determine whether there was an increased proportion of microscopic colitis among patients taking olmesartan.

Statistical Analyses

For the primary outcome, we performed multiple logistic regression, controlling for age and sex, and calculated adjusted odds ratios (ORs) and their corresponding 95% CIs. All reported *P* values are 2-sided. We used SAS version 9.2. When comparing the use of olmesartan among cases diagnosed with celiac disease or microscopic colitis, we used the Fisher exact test. The Institutional Review Board at Columbia University Medical Center approved this study.

RESULTS

We identified 2088 patients undergoing EGD and 12,428 patients undergoing colonoscopy who met the inclusion criteria. Cases as defined by those undergoing endoscopy because of diarrhea were 393 (19%) in the EGD and 867 (7%) in the colonoscopy cohort (Table 1). Women composed 65% and 59% of the EGD and

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www.mayoclinicproceedings.org

colonoscopy groups, respectively. Most patients were aged between 50 and 69 years (range, 50-93 y). The proportion of patients taking any antihypertensive was 46% (968/2088) of the patients in the EGD group and 42% (5267/12428) of the patients in the colonoscopy group. The use of olmesartan in particular was reported by 22 (1%) of the EGD and 83 (0.7%) of the colonoscopy study patients, while use of nonolmesartan ARB was reported by 228 (11%) of the EGD and 1048 (8%) of the colonoscopy patients.

Univariate (Table 2) and multivariate (Table 3) analyses demonstrated that there was no statistically significant association between the use of olmesartan and diarrhea among those undergoing EGD (multivariate OR, 1.99; 95% CI, 0.79-5.00) or colonoscopy (multivariate OR, 0.63; 95% CI, 0.23-1.74). Associations that reached statistical significance on multivariate analysis were an increased risk of diarrhea with older age (EGD OR for ≥70 y vs 50-59 y, 1.35; 95% CI, 1.01-1.80; colonoscopy OR, 2.22; 95% CI; 1.86-2.65) and female sex (EGD OR, 1.48; 95% CI, 1.16-1.90; colonoscopy OR, 1.69; 95% CI, 1.45-1.97). In addition, there was a decreased risk of diarrhea among EGD patients taking calcium channel blockers (OR, 0.61; 95% CI, 0.38-0.98) and angiotensin-converting enzyme inhibitors (OR, 0.67; 95% CI, 0.50-0.92) as well

TABLE 1. Characteristics of Study Patients[a,b]

Characteristic	EGD (n=2088)	Colonoscopy (n=12,428)
Age (y)		
50-59	779 (37)	5621 (45)
60-69	763 (37)	4141 (33)
70+	546 (26)	2666 (21)
Sex		
Female	1364 (65)	7387 (59)
Male	724 (35)	5041 (41)
Procedure indication		
Diarrhea (cases)	393 (19)	867 (7)
Reflux (controls)	1695 (82)	-
CRC Screening (controls)	-	11,561 (93)
HTN medications		
None	1120 (54)	7161 (58)
Any	968 (46)	5267 (42)
Olmesartan	22 (1)	83 (0.7)
Any ARB	228 (11)	1048 (8)
Any ACEI	418 (20)	2235 (18)
HCTZ/chlorthalidone	218 (10)	1539 (12)
Beta blocker	404 (19)	2245 (18)
Calcium channel blocker	171 (8)	921 (7)

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; CRC = colorectal cancer; EGD = esophagogastroduodenoscopy; HCTZ = hydrochlorothiazide; HTN = hypertension.
[b]Values are No. (percentage).

TABLE 2. Univariate Analysis of Factors Associated With Diarrhea[a,b]

Factor	EGD			Colonoscopy		
	Diarrhea	Control	P	Diarrhea	Control	P
Age (y)			.38			<.001[c]
50-59	139 (18)	640 (82)		290 (5)[c]	5331 (95)[c]	
60-69	140 (18)	623 (82)		297 (7)[c]	3844 (93)[c]	
70+	114 (21)	432 (79)		280 (11)[c]	2386 (89)[c]	
Sex						
Female	285 (21)[c]	1079 (79)[c]	<.001[c]	608 (8)	6779 (92)[c]	<.001[c]
Male	108 (15)	616 (85)		259 (5)	4782 (95)	
Any antihypertensive	158 (16)[c]	810 (84)[c]	.006[c]	369 (7)	4898 (93)	.91
No antihypertensive	235 (21)	885 (79)		498 (7)	6663 (93)	
Olmesartan	7 (32)	15 (68)	.12	4 (5)	79 (95)	.44
Any ARB	34 (15)	194 (85)	.11	87 (8)	961 (92)	.08
Any ACEI	60 (14)[c]	358 (86)[c]	.009[c]	142 (6)	2093 (94)	.20
HCTZ/chlorthalidone	34 (16)	184 (84)	.20	84 (5)	1455 (95)[c]	.01[c]
Beta blocker	74 (18)	330 (82)	.77	175 (8)	2070 (92)	.09
Calcium channel blocker	22 (13)[c]	149 (87)[c]	.04[c]	66 (7)	855 (93)	.81

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; EGD = esophagogastroduodenoscopy; HCTZ = hydrochlorothiazide.
[b]Values are No. (percentage).
[c]Exposures meeting statistical significance.

TABLE 3. Multivariate Analysis of Factors Associated With Diarrhea[a]

Factor	EGD		Colonoscopy	
	OR (95% CI)	P	OR (95% CI)	P
Age (y)				
50-59	1.0	-	1.0	-
60-69	1.12 (0.86-1.45)	.41	1.44 (1.22-1.71)[b]	<.001[b]
70+	1.35 (1.01-1.80)[b]	.04[b]	2.22 (1.86-2.65)[b]	<.001[b]
Sex				
Female	1.48 (1.16-1.90)[b]	.002[b]	1.69 (1.45-1.97)[b]	<.001[b]
Male	1.0	-	1.0	-
Any antihypertensive	0.72 (0.57-0.90)[b]	.005[b]	0.90 (0.76-1.04)	.14
Olmesartan	1.99 (0.79-5.00)	.14	0.63 (0.23-1.74)	.37
Any ARB	0.73 (0.49-1.09)	.12	1.17 (0.92-1.49)	.20
Any ACEI	0.67 (0.50-0.92)[b]	.01[b]	0.89 (0.73-1.08)	.23
HCTZ/chlorthalidone	0.87 (0.58-1.30)	.49	0.66 (0.51-0.84)[b]	<.001[b]
Beta blocker	1.07 (0.80-1.43)	.66	1.11 (0.93-1.33)	.25
Calcium channel blocker	0.61 (0.38-0.98)[b]	.04[b]	0.97 (0.75-1.27)	.84

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; EGD = esophagogastroduodenoscopy; HCTZ = hydrochlorothiazide.
[b]Exposures meeting statistical significance.

as among colonoscopy patients taking thiazide diuretics (OR, 0.66; 95% CI, 0.51-0.84).

Of the 393 patients who presented for upper endoscopy because of diarrhea, 70 (18%) had biopsy results consistent with celiac disease and 2 (0.5%) of those were taking olmesartan. When compared with EGD patients who presented because of diarrhea without a diagnosis of celiac disease on biopsy, there was no statistically significant association between the use of olmesartan and the diagnosis of celiac disease (P=.61) (Table 4).

Of the 867 patients who presented for colonoscopy because of diarrhea, 762 (88%) underwent biopsy and 59 of these had a diagnosis of microscopic colitis. None of the diagnoses of microscopic colitis, however, was associated with current use of olmesartan (Table 5). When compared with colonoscopy cases without a diagnosis of microscopic colitis on biopsy, there was no statistically significant association between the use of olmesartan and the diagnosis of microscopic colitis (P=1.0).

TABLE 4. Antihypertensive Use in EGD Cases With/Without Diagnosis of Celiac Disease on Biopsy[a,b]

Antihypertensive	Diagnosis celiac disease (n=70)	No diagnosis celiac disease (n=323)
HTN medication, any	23 (33)	135 (42)
Olmesartan[c]	2 (3)	5 (2)
Any ARB	2 (3)	32 (10)
Any ACEI	11 (16)	49 (15)
HCTZ/chlorthalidone	7 (10)	27 (8)
Beta blocker	10 (14)	64 (20)
Calcium channel blocker	2 (3)	20 (6)

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; HCTZ = hydrochlorothiazide; HTN = hypertension.
[b]Values are No. (percentage).
[c]P=.61.

DISCUSSION

In this case-control study, we sought to examine the recently described association between the use of olmesartan and chronic severe diarrhea using a large sample of patients presenting for endoscopy at a tertiary referral medical center. Previous data on the risk of diarrhea among individuals taking olmesartan come from the original trial comparing the use of olmesartan to placebo in patients with diabetes. Data from that trial suggested no increased gastrointestinal adverse effects of the drug; however, the risk of diarrhea with the use of olmesartan was not a primary end point of the study.[7] To our knowledge, this is the first study to compare the rate of use of olmesartan and biopsy findings in patients with symptomatic chronic diarrhea vs asymptomatic individuals presenting for endoscopic evaluation.

We found that neither olmesartan nor other ARBs were associated with diarrhea among patients undergoing endoscopy. Other antihypertensives were negatively associated with diarrhea, possibly as a result of their known constipating effects. Analysis of the biopsy results of those patients who presented for endoscopy because of diarrhea similarly resulted in negative findings: there was no statistically significant association between patients whose biopsy results were consistent with a diagnosis of celiac disease or microscopic colitis and the use of olmesartan. Notably, most of the individuals in the initial case series who developed sprue-like enteropathy associated with the use of olmesartan were HLA DQ2 or DQ8 positive, suggesting potential predisposing factors in certain individuals; however, the underlying mechanism remains unknown.

Strengths of this study include the large sample size as well as the comprehensive and protocoled, direct, in-person solicitation of home medication use immediately preceding each endoscopic procedure. Limitations of this study include its retrospective nature, although it examines a large sample size for a rare event

that may not be amenable to a prospective design. There was also a relatively small prevalence of use of olmesartan (0.7%-1%) among study patients, limiting the power of this analysis. Because the upper bound of our 95% CI was 5.00 in the EGD analysis and 1.74 in the colonoscopy analysis, a meaningful association between olmesartan and diarrhea may exist that was not detectable because of the relative rarity of use of olmesartan.

CONCLUSION

Our findings suggest that the spruelike enteropathy recently associated with olmesartan is a rare event and milder presentations causing diarrhea among substantial numbers of outpatients are unlikely. Future studies should focus on the mechanisms by which olmesartan causes severe spruelike enteropathy, and the identification of patient-related risk factors that predispose for this rare but serious outcome.

Abbreviations and Acronyms: **ARB** = angiotensin receptor-blocker; **EGD** = esophagogastroduodenoscopy; **OR** = odds ratio

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TABLE 5. Antihypertensive Use in Colonoscopy Cases With/Without Microscopic Colitis on Biopsy[a,b]

Antihypertensive	Microscopic colitis (n=59)	No microscopic colitis (n=703)
HTN medication, any	24 (41)	296 (42)
Olmesartan[c]	0 (0)	4 (0.6)
Any ARB	5 (8)	71 (10)
Any ACEI	13 (22)	109 (16)
HCTZ/chlorthalidone	6 (10)	63 (9)
Beta blocker	8 (14)	137 (19)
Calcium channel blocker	2 (3)	53 (8)

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; HCTZ = hydrochlorothiazide; HTN = hypertension.
[b]Values are No. (percentage).
[c]P=1.0.

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EXHIBIT 16

Olmesartan-Associated Enteropathy

A Review of Clinical and Histologic Findings

Eun-Young Karen Choi, MD; Barbara J. McKenna, MD

• Olmesartan is an antihypertensive medication belonging to the angiotensin II receptor blocker class of drugs that has recently been associated with severe enteropathy. Olmesartan-associated enteropathy is uncommon and may be difficult to recognize because of its clinical and histologic similarities to other clinical entities, including celiac sprue and autoimmune enteropathy. The purpose of this article is to review the clinical and histologic findings of olmesartan-associated enteropathy that have been reported in the literature and to discuss clinical entities to consider in the differential diagnosis of olmesartan-associated enteropathy.

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Olmesartan medoxomil (trade name Benicar), the prodrug of olmesartan, is an angiotensin II receptor blocker (ARB) that was approved for use in the United States as an antihypertensive medication in 2002.[1,2] Other drugs containing olmesartan include Benicar HCT (olmesartan medoxomil/hydrochlorothiazide), Azor (olmesartan/amlodipine), and Tribenzor (olmesartan/amlodipine/hydrochlorothiazide).

Rubio-Tapia et al[3] were the first to report an association between olmesartan use and the development of unexplained severe enteropathy in 2012. In July 2013, the Food and Drug Administration approved changes to drug labels containing olmesartan to include a warning that olmesartan could cause a "sprue-like enteropathy."[1] There are approximately 100 cases currently reported in the English-language literature that support olmesartan-associated enteropathy (OAE) as a distinct clinical entity.[3–20]

The aim of this article is to provide a review of clinicopathologic findings of OAE with a focus on microscopic features of gastrointestinal tract biopsies described in the literature as well as to provide a brief discussion of other entities to consider in the differential diagnosis of OAE. Original case reports and series published in the English-language literature of patients who developed enteropathy while on olmesartan therapy were identified through electronic searches in PubMed as well as manual bibliographic searches.

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CLINICAL AND LABORATORY FINDINGS

Based on cases reported to date,[3–20] OAE affects both men and women equally, and it most frequently affects patients in the seventh to eighth decades of life (mean age, 68 years; range, 46–91 years). Most patients with OAE present with chronic nonbloody diarrhea and weight loss.[3,10] Other commonly reported symptoms are fatigue, nausea, vomiting, abdominal pain, and bloating.[10] Patients typically develop symptoms months to years after initiation of olmesartan therapy. In the series by Rubio-Tapia et al,[3] the average duration of exposure to olmesartan was 3.1 years (range, 0.5–7 years).[3] Hospitalization and possibly admission to the intensive care unit may be required for severe symptoms, including severe dehydration, acute renal failure, electrolyte imbalance, and the need for parenteral nutrition.[3,10]

The most frequently reported laboratory abnormalities are normocytic normochromic anemia and hypoalbuminemia.[10] Celiac serology results have been negative in all reported patients tested for anti-transglutaminase, anti-gliadin, or anti-endomysial antibodies.

Detection of anti-enterocyte antibodies[3] and antinuclear antibodies[11] has been reported in a few cases. Either HLA-DQ2 or HLA-DQ8 was identified in 45 of 65 individuals (69%) with OAE, most of whom showed HLA-DQ2.*

Workup for infectious causes of chronic diarrhea is negative in nearly all reported cases of OAE. One patient was reported to have *Clostridium difficile* in a stool sample,[16] and *Helicobacter pylori* gastritis was reported in another patient.[3] These patients' symptoms, however, completely resolved only after discontinuation of olmesartan. Small-bowel bacterial overgrowth was detected in at least 13 patients with OAE,[3,13] but resolution of symptoms did not occur with antibiotic treatment.

IMAGING AND ENDOSCOPIC FINDINGS

Imaging and endoscopic findings in the gastrointestinal tract may reveal no significant abnormalities. Reported

* *References 3, 6, 7, 9, 10, 13, 15, 18–20.*

imaging abnormalities include diffuse edema and bowel wall thickening of the small intestine[16,20] and enlarged abdominal lymph nodes.[16,19] Reported abnormal endoscopic features of the small bowel include mucosal nodularity, villous atrophy, and ulceration.[5,10,11,14,17,18,20]

MICROSCOPIC FINDINGS

The most frequently reported microscopic finding in duodenal biopsies from patients with OAE is villous architectural distortion. Of the cases we identified in the literature with duodenal biopsies, 92 of 100 individuals (92%) had total or partial villous blunting (Figures 1 and 2).[3,5–20] A total of 5 biopsies (5%) had normal duodenal villous architecture,[11,14] 2 of which had increased intraepithelial lymphocytes.[11] Villous architecture was not specified in 3 biopsies.[6]

Increased intraepithelial lymphocytes (IELs) and subepithelial collagen thickening are also commonly reported findings in duodenal biopsies. Increased IELs were reported in 61 of 100 biopsies (61%), ranging from 25 to more than 100 lymphocytes per 100 enterocytes (Figure 3).[3,5–9,11–17,19] Subepithelial collagen thickening was reported in 22 of 100 biopsies (22%; Figures 4 and 5).[3,6,11,12] Variable degrees of lamina propria chronic inflammation, acute inflammation, and increased eosinophils may be present.[3,13,14] No aberrant or clonal lymphocytes have been detected by immunohistochemical stains[3,11,12,16] or T-cell receptor gene rearrangement polymerase chain reaction assay.[3,11]

Microscopic involvement of other gastrointestinal tract sites may also be seen in OAE. Ulcers or microscopic features of lymphocytic and/or collagenous gastritis have been reported in stomach biopsies (Figure 6).[3,19] Described findings in the jejunum[13] and terminal ilium[8,16] include villous blunting, subepithelial collagen thickening, increased IELs, crypt apoptosis, crypt hyperplasia, and lamina propria chronic inflammation with increased eosinophils. Colon biopsies may show increased IELs, subepithelial collagen thickening (Figure 7), and lamina propria chronic inflammation that can resemble lymphocytic or collagenous colitis.[3,5,8,11,13,16–19] Colonic crypt apoptoses have also been described.[8]

It is unknown whether microscopic changes can be seen in the biopsies of patients with OAE prior to the development of severe diarrhea. Lagana et al[21] published a retrospective cohort study to investigate whether any histopathologic changes could be identified in duodenal biopsies of patients who experienced abdominal pain without diarrhea while taking olmesartan (n = 20) or other ARBs (n = 20). No single histopathologic finding was statistically more frequent in patients taking olmesartan compared with age- and sex-matched controls. The authors, however, noted a trend toward significance in the finding of at least one spruelike microscopic feature in the patients taking olmesartan but not in those taking other ARBs, and they raised the possibility that there may be a spectrum of changes with olmesartan use. This study, however, was limited by small sample size and lack of follow-up information regarding patient outcomes.

DIAGNOSIS, TREATMENT, AND OUTCOME

Patients often receive a diagnosis and are treated for other causes of enteropathy before a diagnosis of OAE is given; these other causes are most commonly celiac sprue or autoimmune enteropathy. A presumptive diagnosis of OAE is made in patients who develop symptoms while taking olmesartan, who have supportive histologic findings on gastrointestinal biopsies, and for whom other causes of diarrhea and weight loss have been excluded.

Discontinuation of olmesartan has been the mainstay of treatment. Clinical resolution of diarrhea often occurs within a week of stopping olmesartan. Patients with OAE are typically unresponsive to a gluten-free diet and do not experience symptomatic recurrence after restarting a gluten-containing diet.[3,6,16] Symptomatic improvement is reported in some patients treated with steroids or other immunosuppressant therapy prior to receiving a diagnosis of OAE.[6,11,17] No fatalities have been reported.

Histologic improvement was reported in all 46 patients with follow-up biopsies.[3,5,6,8–12,14,18] Normal villous architecture was reported in 41 of 46 follow-up biopsies (89%) that were obtained 2 months or more after cessation of olmesartan therapy in patients who previously had complete or partial villous blunting.[3,5,8–12,14,18] Two patients with previous biopsies demonstrating complete villous blunting had partial villous blunting at 2-month follow-up.[3,10] The degree of improvement in villous architecture was not specified in the remaining 3 cases.[6,10] Increased IELs were noted in the follow-up biopsy in one of the patients with normal villous architecture.[14] The presence of increased IELs or thickened subepithelial collagen was not reported in any of the 21 follow-up biopsies obtained from patients who had either of these features on prior biopsies.[3,5,6,8,9,11,12]

COMMENT

Establishing a causal relationship in drug-induced enteropathy is difficult. Although deliberate rechallenge with olmesartan to prove causality following withdrawal and symptomatic improvement is not usually attempted given the severity of symptoms, symptomatic recurrence following reintroduction of olmesartan has been documented. Gallivan and Brown[8] reported a case of a patient with severe diarrhea whose clinical symptoms resolved upon discontinuation of both olmesartan and atorvastatin. Upon selectively reintroducing olmesartan to determine which drug was causing the patient's symptoms, the patient had a recurrence of diarrhea. DeGaetani et al[6] also reported on a patient with symptomatic improvement off olmesartan who had recurrence of symptoms upon rechallenge with the medication. Furthermore, there are several reports of olmesartan interruptions done prior to knowledge or diagnosis of OAE (usually motivated by hypotension) that resulted in resolution of diarrhea while off olmesartan and subsequent relapse after restarting olmesartan therapy.[3,11,14]

DeGaetani et al[6] studied 72 patients with "seronegative villous atrophy" at a tertiary care center; the condition was defined by villous blunting on duodenal biopsy and negative celiac serology results. Interestingly, the two most common diagnoses in these patients were seronegative celiac disease (28%) and medication-related villous blunting (26%), the latter of which was attributed to olmesartan in 16 of 19 cases, and mycophenolate mofetil and methotrexate in the remaining 3 cases.

Current data suggest OAE is likely a rare event in patients taking olmesartan. Menne and Haller analyzed data collected in the ROADMAP study in which diabetic patients had received either 40 mg/d olmesartan (n = 2232) or placebo (n = 2215), and they found no differences in the occurrence of diarrhea or abdominal discomfort between

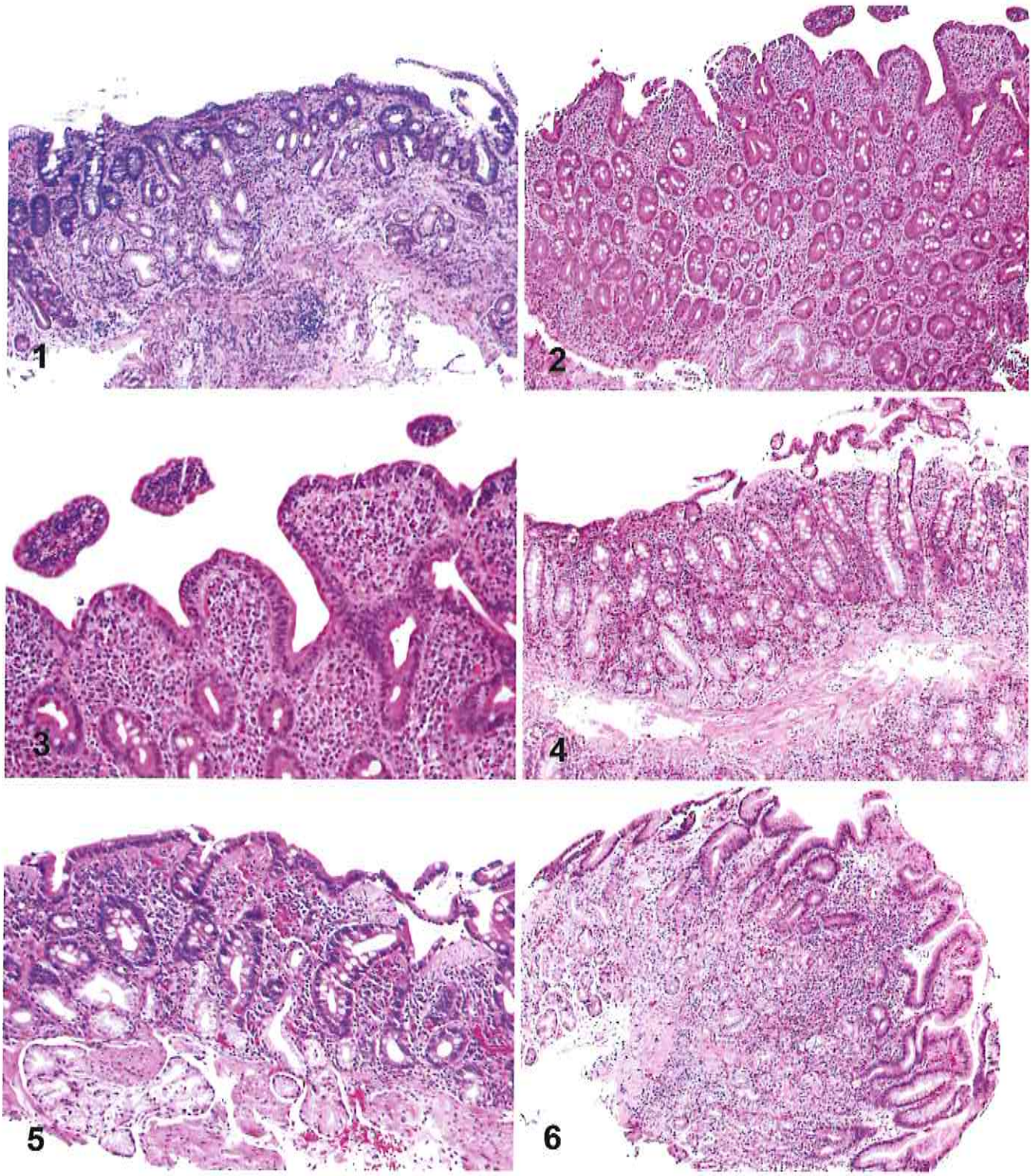

Figure 1. *Olmesartan-associated enteropathy. Duodenum biopsy showing complete villous blunting (hematoxylin-eosin, original magnification ×100). Photo courtesy of Joel Greenson, MD.*

Figure 2. *Olmesartan-associated enteropathy. Duodenum biopsy showing partial villous blunting, lamina propria inflammation extending down to the base of mucosa, and increased intraepithelial lymphocytes (hematoxylin-eosin, original magnification ×100).*

Figure 3. *Olmesartan-associated enteropathy. Higher-power view of Figure 2 duodenum biopsy showing increased intraepithelial lymphocytes and mixed chronic lamina propria inflammation composed of lymphocytes, plasma cells, and eosinophils (hematoxylin-eosin, original magnification ×200).*

Figure 4. *Olmesartan-associated enteropathy. Duodenum biopsy showing complete villous blunting and subsurface collagen deposition with detachment of overlying surface epithelium (hematoxylin-eosin, original magnification ×100).*

these two groups.[22] In the retrospective case-control study by Greywoode et al,[23] analysis of clinical data from patients 50 years and older who had undergone esophagogastroduodenoscopy (n = 2088) or colonoscopy (n = 12 428) procedures found no significant association between olmesartan use and diarrhea. They also found no significant association between olmesartan use and histologic diagnosis of celiac disease or microscopic colitis.[23] The study was limited, however, by the small number of patients taking olmesartan: 22 patients (1%) in the esophagogastroduodenoscopy group and 83 patients (0.7%) in the colonoscopy group.

The mechanism of OAE is currently unknown. The long latency period between initiation of olmesartan and development of symptoms is suggestive of cell-mediated immune damage, and inhibitory effects of ARBs on transforming growth factor β, an important mediator of gut homeostasis, may play a role.[3] Rubio-Tapia et al[3] also propose the possibility that HLA-DQ2 may predispose a person to immune-mediated damage, given that a higher prevalence of HLA-DQ2 is observed in patients with OAE compared with the general population.

Rare cases of enteropathy associated with ARBs other than olmesartan have been reported, suggesting the possibility of ARB class effect. We are aware of only 5 case reports in which patients developed severe enteropathy while taking irbesartan (2 cases),[11,24] valsartan,[25] telmisartan,[24] or eprosartan (only abstract available for review in English).[26] The reported clinicopathologic findings in these patients were similar to those of OAE.

Differential Diagnosis

Autoimmune Enteropathy.—Autoimmune enteropathy (AIE) is a rare cause of intractable diarrhea, malabsorption, and marked weight loss that has histologic features closely resembling those seen in OAE. Akram et al[27] proposed the following 5 criteria to diagnose adult AIE, of which the first 4 are required for diagnosis: (1) adult-onset diarrhea longer than 6 weeks, (2) malabsorption, (3) specific small-bowel histology (partial/complete villous blunting, deep crypt lymphocytosis, crypt apoptotic bodies, minimal surface lymphocytosis), (4) exclusion of other causes of villous atrophy, and (5) presence of anti-enterocyte and/or anti-goblet cell antibodies. Histologic findings of AIE include flattened small-bowel mucosa, prominent crypt epithelial injury, and inflammation composed of lymphocytes, plasma cells, and neutrophils (Figure 8). There may be a loss of Paneth cells and/or goblet cells, and there may be apoptoses, neutrophilic cryptitis, and few surface lymphocytes.[28] The process may be restricted to the small bowel or involve the entire gastrointestinal tract. Patients with OAE may present with clinical findings similar to those with AIE; they may also have histologic features similar to patients with AIE. In fact, the two entities may be indistinguishable histologically, unless the subsurface collagen that is a feature of some cases of OAE is present. Thus, before suggesting a diagnosis of AIE, it is prudent to investigate the patient's clinical history and medication list. If the patient has been taking an olmesartan medoxomil–containing preparation, it would make sense to discontinue the medication and observe for clinical improvement before undertaking immunosuppressive therapy that may be indicated for AIE.

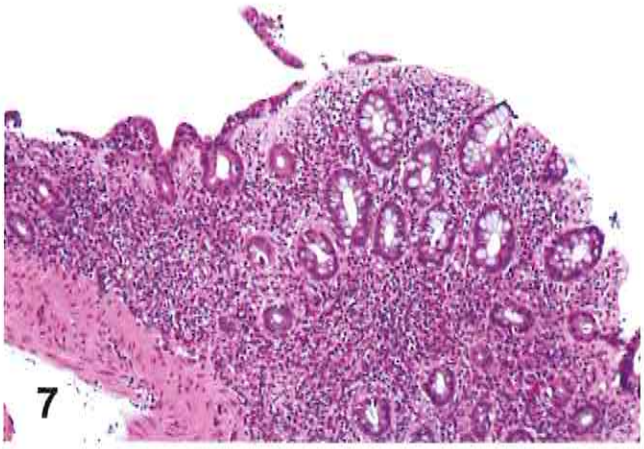

Figure 7. *Olmesartan-associated enteropathy. Colon biopsy with irregular thickening of subepithelial collagen, increased intraepithelial lymphocytes, lamina propria chronic inflammation extending down to crypt bases, and destruction of crypt epithelium (hematoxylin-eosin, original magnification ×100). Photo courtesy of Joel Greenson, MD.*

Celiac Sprue.—In fully developed sprue, the small-bowel mucosa is completely flat, with a very cellular lamina propria and regenerative epithelium,[29] all features that are also found in OAE. There is prominent surface epithelial lymphocytosis, more striking than in most cases of OAE, and cytoplasmic lipid droplets are often present in the surface epithelium (Figure 9).[28] Celiac sprue lacks the apoptotic bodies that are sometimes found in OAE and has less deep mucosal active inflammation and epithelial injury. Most cases also lack the subsurface collagen that may be present in OAE, although this may be present in the related entity, collagenous sprue.[28] Again, clinical features are extremely helpful in arriving at the appropriate diagnosis, specifically the serologic tests associated with gluten sensitivity that have positive results in patients with celiac disease and negative results in those with OAE, and the lack of history of olmesartan use. The findings of celiac disease are generally restricted to the small bowel, although lymphocytic or collagenous gastritis and/or lymphocytic or collagenous colitis may be present in some patients.

Graft-Versus-Host Disease.—Patients with bone marrow transplants who develop gastrointestinal graft-versus-host disease (GVHD) that affects the small bowel may have variable degrees of mucosal architectural distortion, depending on the grade and duration of the GVHD injury. Findings are often subtle, with mild villous blunting, loss of crypts, and apoptosis (Figure 10).[30] In some cases, however,

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Figure 5. *Olmesartan-associated enteropathy. Higher-power view of a duodenal biopsy showing flattened villous mucosa and an irregular band of subepithelial collagen with detachment of overlying surface epithelium (hematoxylin-eosin, original magnification ×200).*

Figure 6. *Olmesartan-associated enteropathy. Stomach biopsy with microscopic features of collagenous gastritis. There is irregular thickening of subsurface collagen (left side of photo) and chronic lamina propria inflammation (hematoxylin-eosin, original magnification ×100).*

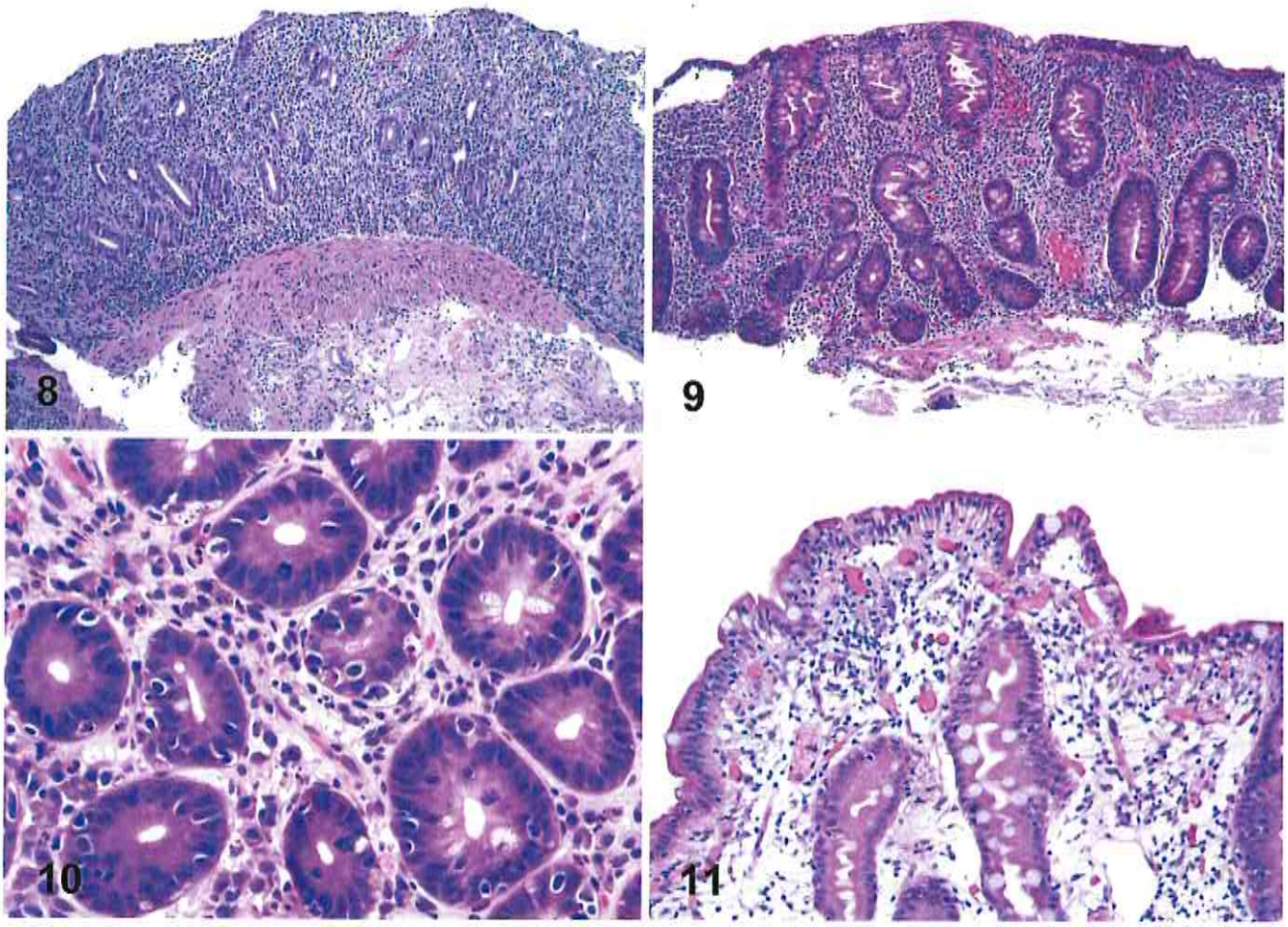

Figure 8. *Autoimmune enteropathy. Small intestine biopsy with complete villous blunting, chronic inflammation, prominent crypt epithelial injury, and loss of Paneth cells and goblet cells (hematoxylin-eosin, original magnification ×100).*

Figure 9. *Celiac sprue. Small intestine biopsy showing fully developed sprue with complete flattening of villi, prominent surface epithelial lymphocytosis, and lamina propria inflammation composed of lymphocytes and plasma cells. Cytoplasmic lipid droplets are present in the surface epithelium (hematoxylin-eosin, original magnification ×100).*

Figure 10. *Graft-versus-host disease. Small intestine biopsy showing prominent apoptotic cells (hematoxylin-eosin, original magnification ×400).*

Figure 11. *Common variable immune deficiency. Small intestine biopsy with villous blunting and increased intraepithelial lymphocytes but no plasma cells in the lamina propria (hematoxylin-eosin, original magnification ×200).*

GVHD may lead to flat small-bowel mucosa when there is significant crypt injury. The lamina propria tends to be relatively paucicellular, and a case of GVHD that has significant mucosal flattening would likely have more prominent apoptosis than OAE. Surface lymphocytosis and subsurface collagen deposition are not features of small-bowel GVHD. As with all of the entities in the differential diagnosis of OAE, clinical history is key in establishing the correct diagnosis.

Common Variable Immune Deficiency.—Patients with common variable immune deficiency may have abnormalities throughout the gastrointestinal tract, including flattened small-bowel mucosa, prominent lymphoid aggregates, apoptoses, increased IELs, collagenous changes, and infections (eg, cytomegalovirus, *Cryptosporidium*, *Candida*, *Giardia*).[28] Some of these features, such as the villous blunting, apoptosis, and increased IELs, are also seen in OAE, resulting in somewhat similar histology. However, OAE does not generally have prominent lymphoid aggregates or frequent mucosal infections. The paucity of plasma cells in the lamina propria of patients with common variable immune deficiency (present in more than two-thirds of cases) is a key finding in making the histologic diagnosis or suggesting appropriate testing for common variable immune deficiency (Figure 11). Patients with common variable immune deficiency usually present at younger ages than those with OAE, often in the second and third decades of life, an age range in which olmesartan use would be unusual.

Bacterial Overgrowth.—Abnormal proliferations of enteric bacteria may occur in the small bowel for a variety of reasons, including dysmotility, hypochlorhydria, blind loops, and myopathies.[31] Patients with bacterial overgrowth may present with malabsorption, diarrhea, anemia, and abdominal pain. Histologic features that resemble those of OAE include variable villous blunting and cellular lamina

propria. Surface lymphocytosis and sometimes neutrophils may be clues to consider bacterial overgrowth. Subsurface collagen deposition and apoptoses are not generally prominent features. Clinical findings, including history of diseases associated with motility disorders (eg, connective tissue diseases, diabetic neuropathy, Parkinson disease), other gastrointestinal tract diseases, or prior operations, should prompt consideration of bacterial overgrowth in the setting of an otherwise nonspecifically abnormal small-bowel biopsy, and medication history is important in ruling out OAE. It is interesting to note that concurrent small-intestinal bacterial overgrowth was observed in several patients with OAE,[3,13] but symptoms only fully resolved with discontinuation of olmesartan.

CONCLUSIONS

Olmesartan-associated enteropathy is a rare cause of severe enteropathy that should be considered in the differential diagnosis of patients with unexplained chronic diarrhea who are taking olmesartan-containing medications. Microscopic findings may be limited to the small intestine or show diffuse involvement of the entire gastrointestinal tract. Although the microscopic findings are not specific, they can be helpful in suggesting the diagnosis of OAE in the right clinical setting.

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EXHIBIT 17

Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes Mellitus

Retrospective Cohort Study

Raj Padwal, Mu Lin, Mahyar Etminan, Dean T. Eurich

Abstract—Olmesartan has been linked with increased risk of cardiovascular mortality and sprue-like enteropathy. We compared outcomes between olmesartan and other angiotensin receptor blockers in a large clinical registry of patients with diabetes mellitus. A retrospective cohort analysis using nationwide US-integrated insurance and laboratory claims was performed in 45 185 incident diabetic angiotensin receptor blocker users, including 10 370 (23%) olmesartan users. Hazard ratios were computed using time-dependant Cox models adjusted for sociodemographic characteristics, comorbidities, laboratory data, drug use, healthcare utilization, and the propensity to receive olmesartan. Blood pressure data were unavailable. Subjects were followed up for 116 721 patient-years. The primary end point was all-cause hospitalization or all-cause mortality and occurred in 10 915 (24%) patients. Average age was 54.3±9.6 years, 52% were men, 17% had cardiovascular disease, and 10% chronic kidney disease. Compared with other angiotensin receptor blockers, the adjusted hazard for olmesartan was 0.99 (95% confidence interval, 0.94–1.05) for all-cause hospitalization and mortality; 0.90 (0.62–1.30) for all-cause mortality; 0.99 (0.94–1.05) for all-cause hospital admission; 0.88 (0.78–1.00) for cardiovascular disease–related admission, and 1.09 (0.98–1.20) for gastrointestinal disease–related hospitalization in the overall cohort. Olmesartan use was associated with an adjusted hazard for the primary outcome of 1.11 (0.99–1.24) in subjects with history of cardiovascular disease and 1.21 (1.04–1.41) in subjects with chronic kidney disease. In conclusion, there is no robust signal for harm with olmesartan use. Risk may be increased in kidney disease; thus, given the widespread availability of alternate agents, olmesartan should be used with caution in this subgroup pending further study. **(*Hypertension*. 2014;63:977-983.) • Online Data Supplement**

Key Words: angiotensin receptor antagonists ■ cardiovascular diseases ■ comparative effectiveness research ■ hospitalization ■ mortality ■ olmesartan

Olmesartan, an angiotensin II type 1 receptor antagonist (ARB) first approved in 2002, is commonly used for the treatment of hypertension.[1] Despite being the seventh ARB approved by the Food and Drug Administration and despite a lack of hard outcome trial data supporting its use, olmesartan is widely prescribed, with estimated worldwide sales of 2 billion US dollars in 2009.[2] Two placebo-controlled randomized controlled trials examining the efficacy of olmesartan in delaying onset/progression of renal disease in patients with diabetes mellitus, Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy (ORIENT), have been recently published.[3,4] In both trials, cardiovascular mortality was increased in subjects randomized to olmesartan treatment. In ROADMAP, cardiovascular deaths occurred in 15 (0.7%) olmesartan-treated subjects and 3 (0.1%) placebo-treated subjects (P=0.01). In subjects with pre-existing cardiovascular disease taking olmesartan, 11 cardiovascular deaths occurred compared with 1 in subjects assigned to placebo. In ORIENT, 10 (3.5%) subjects receiving olmesartan died of cardiovascular causes compared with 3 (1.1%) placebo-treated subjects (P>0.05). Although these data raise concerns, they do not definitively prove harm because cardiovascular death was not a primary end point, the absolute number of cardiovascular events was low in both studies, and nonfatal cardiovascular events were not significantly different between study arms in ROADMAP (81 [3.6%] for olmesartan versus 91 [4.1%] for placebo; P=0.31).

After undertaking a safety review of olmesartan in 2011, the US Food and Drug Administration determined that the benefits of the drug outweighed its potential risks in patients with hypertension but advised against use of olmesartan for

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delaying or preventing renal disease and underscored the need for more postmarketing surveillance.[5] In 2013, following case reports describing a potential association between olmesartan and sprue-like enteropathy, the Food and Drug Administration issued a second warning and announced plans to conduct further safety reviews.[6]

The objective of this study was to provide further postmarketing assessment of the comparative effectiveness and safety of olmesartan. Specifically, we assessed the effect of olmesartan therapy compared with other ARBs on overall mortality and cause-specific hospitalization and sought to quantify absolute event rates. Given prior evidence, we hypothesized that olmesartan use would increase the risk of mortality or hospitalization relative to other ARBs in patients with diabetes mellitus, and that this risk increase would be highest in patients with pre-existing cardiovascular disease and chronic kidney disease (CKD; ie, high-risk subgroups).

Methods

We performed a population-based retrospective cohort study using an anonymized large US claims and integrated laboratory database containing information on employed, commercially insured patients with dependants from all 50 states (Clinformatics Data Mart, Optum, Life Sciences). The database has been used in multiple previous studies, contains >13 million annual lives.[7–10] We analyzed patient-level, clinically rich, deidentified longitudinal data, including administrative and demographic information (sex, age, type of insurance plan, eligibility date, and income); billable medical service inpatient, outpatient, and medical procedure claims (deidentified physician and facility identifier, date and place of service, cost of service, admission and discharge dates, procedure, and diagnosis codes); and laboratory test results and pharmacy claims data (deidentified prescribing physician, drug dispensed based on national drug codes, quantity and date dispensed, drug strength, days' supply, and cost of service). *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) clinical and procedure codes were used, and data were cleaned and analyzed using protocols compliant with the Health Insurance Portability and Accountability Act.

Research ethics review board approval to conduct this study was obtained from the University of Alberta and the New England Institutional Review Board. The procedures followed were in accordance with institutional guidelines.

Cohort Selection

An inception cohort of 114 010 new ARB users with diabetes mellitus aged ≥20 years and identified between January 1, 2004 and December 31, 2009 was created. The date of the first ARB prescription was designated as the index date. New users were individuals who did not have a prior prescription claim for any ARB for ≥1 year before their index date. We limited inclusion to subjects with ≥1 year of baseline data enrolled in a commercial medical insurance plan (Figure 1). Subjects were followed up until death, termination of medical insurance, or December 31, 2010 (study end) providing a maximum follow-up of 6 years. A priori, we decided to exclude users who crossed over from olmesartan to another ARB (or vice versa) during the follow-up period (n=3257). Mortality was ascertained by linking to the US national death index file.[11] This is a highly valid and reliable method, with >98% sensitivity when social security number data are available.[12]

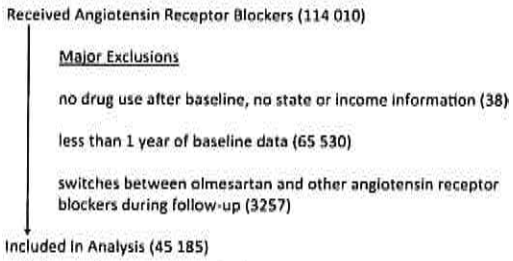

Figure 1. Inclusions and exclusions.

The primary outcome was all-cause hospital admission or death. This composite outcome was analyzed using time-to-first event (eg, either admission date or date of death) as the dependent variable. Each component of this composite end point was also analyzed separately. Cause-specific mortality was not available. Other secondary end points included cardiovascular-related hospital admissions (*ICD-9-CM* codes 410, 411.1, 428, 430–438), the combined end point of cardiovascular-related hospital admission or all-cause mortality, gastrointestinal-related hospital admissions (*ICD-9-CM* codes 530–579), and admissions related to noninfective enteritis and colitis (*ICD-9-CM* codes 555–558). Patients were censored if they did not have an outcome of interest and reached study end (December 31, 2010) or their insurance was terminated.

Analyses

Time-varying Cox proportional hazards regression was used to estimate the effect of exposure to olmesartan (relative to all other ARBs) on each outcome. Time zero was set at index date.[13] The days' supplied field in the prescription drug dispensations database was used as a proxy for the expected duration of each prescription and was used to compute time-varying drug exposure.[14] We assumed that subjects were exposed to the drug of interest unless prescription refills were not obtained for 2 consecutive days' supplied periods. If drug discontinuation occurred, subjects were classified as unexposed from the end of the first consecutive days' supplied period to the end of the study or until they restarted the drug. In this time-varying primary analysis, outcome events were attributed to a given drug if the event occurred while the subject was exposed; no legacy or carryover effects from remote exposure were assumed.

Covariates

In addition to using time-varying exposure models to limit potential bias, additional potential confounders were included in the Cox regression models as time fixed baseline variables. These included age, sex, socioeconomic status (type of medical insurance and median household income according to the 2010 US census),[15] cardiovascular comorbidities, clinical laboratory data (glycohemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate [according to the Modified Diet in Renal Disease calculation: ≥90, 89.9–60, 59.9–30, <30 mL/min], albuminuria, and hemoglobin concentrations), and prescription drugs (eg, antidiabetic agents, antiplatelet drugs, anticoagulants, statins, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates). For patients who did not have specific clinical laboratory data measured, we used the missing indicator approach for all analyses.[16]

To further control for baseline comorbidity and illness, we included an Adjusted Clinical Groups score in the model. This single comorbidity score is derived from the Johns Hopkins Adjusted Clinical Groups score system (Version 9)[17] and is weighted by 32 adjusted diagnostic groups. It performs equally to or better than the Charlson and Elixhauser comorbidity scores.[18] In addition, we adjusted for the total number of hospital admissions in the year before the index date, the total number of chronic conditions at baseline, frailty (any occurrence of malnutrition, abnormal weight loss, morbid obesity, dementia, falls, and decubitus ulcer),[17] and the time-varying propensity to receive olmesartan. For the latter, we computed the updated propensity or probability of receiving olmesartan every 3 months throughout the follow-up period.[19] This propensity score was entered into the model as a continuous probability score that was based on ≈60 variables, including demographic variables (age, sex, age–sex interaction, state, and type of insurance), socioeconomic factors (income), comorbidities, health service use, laboratory data, markers of frailty, and drug treatments. A full list of model covariates and variables included in the propensity score is available on request.

Subgroup and Sensitivity Analyses

Subgroup analyses were performed in subjects with a baseline history of cardiovascular disease and with CKD (defined as an estimated glomerular filtration rate <60 mL/min). A sensitivity analysis in which we repeated primary analysis comparing olmesartan with all other ARBs but censored subjects who switched from one ARB class to another (instead of excluding them) was also performed.

A dose–response analysis and an analysis comparing olmesartan with individual ARBs were also performed. Further methodological details are provided in the online-only Data Supplement.

Results

Of 114 010 ARB users, the final cohort comprised 45 185 subjects (Figure 1). Mean age was 54.3 (SD, 9.6) years, 52% were men, 17% had a history of cardiovascular disease, 13% had diabetes mellitus–related complications, and 10% had CKD (Table 1). We identified 10 370 (23%) olmesartan users and 34 815 (77%) who used other ARBs during the follow-up period. Additional baseline characteristics of the study population are summarized in Table 1. The prevalence of concomitant comorbidities was either equal between groups or lower in olmesartan users compared with users of other ARBs. One exception was hypertension, which was more common in olmesartan users. The average daily ARB doses prescribed during the follow-up period were olmesartan 22.1 mg, losartan 52.1 mg, valsartan 110.5 mg, telmesartan 41.9 mg, eprosartan 424.2 mg, irbesartan 145.9 mg, and candesartan 14.1 mg.

Subjects were followed up for 116 721 patient-years (median duration, 2.3 years [interquartile range, 1.1–3.8 years]). The primary composite end point occurred in 10 915 (24%) subjects; 10 836 (24%) subjects experienced ≥1 hospital admission and 458 (1%) died (Table 2).

The crude incidence rates of all-cause hospital admission or all-cause mortality were lower in olmesartan users compared with other ARBs (Table 2). However, after time-varying, multivariable adjustment was performed, the relative hazard of the primary composite end point was similar in olmesartan users (adjusted hazard ratio [aHR], 0.99; 95% confidence interval, 0.94–1.05; Table 2; Figure 2). In addition, compared with other ARB users, aHRs in olmesartan users were 0.90 (0.62–1.30) for all-cause mortality; 0.99 (0.94–1.05) for all-cause hospital admission; and 0.88 (0.78–1.01) for cardiovascular disease–related hospitalization (Table 2).

The covariate-aHR of gastrointestinal disease–related hospitalization was 1.09 (0.98–1.20) for olmesartan users compared with other ARB users and the aHR for admissions related to noninfective enteritis and colitis was 1.21 (0.87–1.69; Table 2).

Subgroup Analyses

Results in high-risk subjects are summarized in Table 3. In subjects with pre-existing cardiovascular disease, the aHR for the primary outcome was 1.11 (0.99–1.24) in olmesartan users. The aHR for the primary outcome was increased in olmesartan users with CKD (aHR, 1.21 [1.04–1.41]).

Sensitivity Analysis Censoring Rather Than Excluding ARB Switchers

In this analysis (n=48 475), the aHRs comparing olmesartan with all other ARBs for the primary outcome were 1.02 (95% confidence interval, 0.97–1.08) in the overall cohort,

Table 1. Baseline Characteristics of Olmesartan and Other ARB Users

	Olmesartan Users (n=10 370)	Other ARB Users (n=34 815)	*P* Value
Age, y	53.7±9.3	54.4±9.7	<0.0001
Sex			0.3709
Men	5472 (53)	18 197 (52)	
Women	4898 (47)	16 618 (48)	
Annual income, US dollars	48 034±6052	48 380±6237	<0.0001
Type of insurance			<0.0001
Point of service	6003 (58)	19 722 (57)	
Exclusive provider	1901 (18)	5956 (17)	
Preferred provider	889 (9)	3399 (10)	
Health maintenance	1463 (14)	5267 (15)	
Independent	108 (1)	455 (1)	
Other	6 (0)	16 (0)	
Clinical parameters at baseline			
Adjusted Diagnostic Groups Comorbidity Score	11±9	13±10	<0.0001
History of CV disease			
Ischemic heart disease	1425 (14)	6400 (18)	<0.0001
Heart failure	333 (3)	2065 (6)	<0.0001
Myocardial infarction	89 (1)	645 (2)	<0.0001
Dyslipidemia	6270 (60)	20 823 (60)	0.2339
Hypertension	9067 (87)	38 745 (83)	<0.0001
Arrhythmia	535 (5)	2463 (7)	<0.0001
Valvular heart disease	400 (4)	1698 (5)	<0.0001
eGFR categories, mL/min			<0.0001
<30	50 (0.5)	388 (1)	
30 to <60	824 (8)	3313 (10)	
60 to <90	5768 (56)	18 564 (53)	
≥90	3728 (36)	12 500 (36)	
Albuminuria (≥5 g/dL)	612 (6)	2533 (7)	<0.0001
Total cholesterol, mg/dL	192±46	190±46	0.0023
Triglycerides, mg/dL	181±174	180±195	0.7589
HDL, mg/dL	47±13	48±14	0.1175
LDL, mg/dL	112±37	109±37	0.0008
A1c, %	7.1±1.7	7.3±1.8	<0.0001
Hemoglobin, g/dL	14.1±1.6	13.9±1.6	<0.0001
Medication use			
Metformin	3404 (32)	11 988 (34)	0.0024
Sulfonylureas	1956 (19)	7525 (22)	<0.0001
Thiazolidinediones	1579 (15)	5951 (17)	<0.0001
Insulin	1032 (10)	4511 (13)	<0.0001
RAS blocker (ACE inhibitor or direct renin inhibitor)	4148 (40)	13 509 (39)	0.0282
Statins	4026 (39)	13 689 (39)	0.3641
β-Blockers	2610 (25)	9384 (27)	0.0003
Dihydropyridine CCB	1805 (17)	5494 (16)	<0.0001
Non-dihydropyridine CCB	602 (6)	2119 (6)	0.2906
Nitrates	336 (3)	1545 (4)	<0.0001

(Continued)

Table 1. Continued

	Olmesartan Users (n=10 370)	Other ARB Users (n=34 815)	P Value
Diuretics	2641 (25)	8574 (24)	0.0820
Anticoagulants	227 (2)	1073 (3)	<0.0001
Antiplatelets	459 (4)	2157 (6)	<0.0001
Healthcare utilization			
Inpatient hospitalization in year before index?			<0.0001
0	9473 (91)	30 438 (87)	
1	744 (7)	3404 (10)	
≥2	153 (1)	973 (3)	
Frailty	429 (4)	1536 (4)	0.2282
Chronic conditions in year before index date			<0.0001
≤1	1900 (18)	6373 (18)	
2–5	6653 (64)	20 540 (59)	
≥5	1817 (18)	7902 (22)	
Medication possession ratio for DM-related medications	0.44±0.7	0.47±1.0	0.0005

Data are n (%) or mean±SD. A1c indicates hemoglobin A1c; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and RAS, renin angiotensin system.

1.07 (0.93–1.24) in pre-existing cardiovascular disease, and 0.91 (0.82–1.01) in CKD.

Dose–Response Sensitivity Analyses

Results of the dose–response analysis are summarized in Table S1 in the online-only Data Supplement. In the overall cohort and in the cardiovascular disease subgroup, higher doses of olmesartan were associated with significantly increased risk for the primary outcome. The dose–response analyses for valsartan showed similar results to olmesartan. However, the dose–response analysis for losartan did not show increasing risk with higher doses (Table S1).

Results of the analysis comparing individual ARB agents are summarized in Table S2. In this sensitivity analysis, olmesartan was not consistently associated with the highest risk of harm. Few statistically significant differences were found between agents. Exceptions were that losartan was associated with a borderline statistically significant increase in the primary end point in subjects with cardiovascular disease, and the other ARBs (candesartan, eprosartan, and irbesartan) were associated with a lower risk for the primary end point in the CKD subgroup only (Table S2). In both cases, this result was driven by significant reductions in hospitalizations but not mortality (data not shown).

Discussion

In this analysis of a clinically rich data set encompassing >45 000 patients with diabetes mellitus, after extensive multivariable adjustment, we found that olmesartan use compared with other ARB use was not associated with an increased risk of hospitalization or all-cause mortality in the overall cohort. In fact, there was a trend toward a lower relative hazard for cardiovascular hospitalizations. However, in the higher-risk subjects (those with pre-existing cardiovascular disease or CKD), the aHRs for this primary end point were increased, and this risk increase was statistically significant in subjects with CKD (however, this finding was not robust to sensitivity analysis). The increased risk was primarily driven by an increase in the relative hazard of all-cause hospitalization. When we examined cause-specific hospitalization, we found no statistically significantly increased risk for cardiovascular disease–related and gastrointestinal disease–related hospitalization. A dose–response analysis of olmesartan found an increased risk for the primary end point in the overall cohort and in subjects with cardiovascular disease. However, similar findings were observed in a dose–response analysis for valsartan (but not losartan). This suggests that higher doses might have been a marker of increased risk rather than a causative factor. Finally, in the agent-specific analysis, olmesartan was not consistently associated with the highest risk, and few statistically significant differences between agents were found. In aggregate, our results do not demonstrate a robust signal for harm with olmesartan use in patients with diabetes mellitus, with the possible exception of diabetes mellitus with CKD.

One prior, large retrospective cohort analysis comparing olmesartan with other ARBs has been published.[20] This study of 118 700 subjects enrolled in a single US national healthcare plan reported that olmesartan use was associated with a lower risk of cardiac events compared with valsartan,

Table 2. Outcome Comparisons in Olmesartan Users vs Users of All Other Angiotensin Receptor Blockers

Outcome	Time at Risk (Person-Years)	Events , n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P Value
All-cause hospitalization or mortality	16 040	1686 (16)	0.87 (0.83–0.92)	0.99 (0.94–1.05)	0.89
All-cause mortality	18 310	35 (0.3)	0.67 (0.47–0.97)	0.90 (0.62–1.30)	0.56
All-cause hospitalization	16 040	1678 (16)	0.87 (0.83–0.92)	0.99 (0.94–1.05)	0.91
CV disease–related hospitalization	17 951	311 (3)	0.67 (0.59–0.75)	0.88 (0.78–1.00)	0.051
GI disease–related hospitalization	17 647	498 (5)	0.98 (0.88–1.08)	1.09 (0.98–1.20)	0.10
Noninfective enteritis and colitis-related admissions	18 247	46 (0.4)	1.05 (0.75–1.47)	1.21 (0.87–1.69)	0.26

Models adjusted for age, sex, socioeconomic status, cardiovascular comorbidities, clinical laboratory data, prescription drugs, Adjusted Clinical Groups score, total number of hospital admissions in the year before the index data, total number of chronic conditions at baseline, frailty, and the time-varying propensity to receive olmesartan. CI indicates confidence interval; CV, cardiovascular; GI, gastrointestinal; and HR, hazard regression.

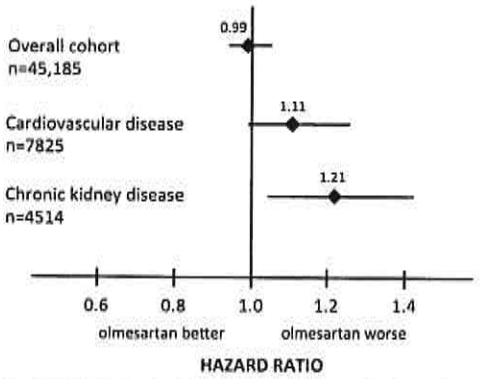

Figure 2. Adjusted hazard ratios and 95% confidence intervals for all-cause hospital admission or all-cause death according to olmesartan exposure.

irbesartan, and losartan. A limitation of this analysis was that olmesartan was prescribed to lower risk individuals, and no propensity score adjustment was used. In addition, the study population was broad and not limited to subjects with type 2 diabetes mellitus and no high-risk subgroup analyses were performed. Thus, although these findings are broadly consistent with the results of our study, they are not directly comparable because of differences in study populations and methodologic approaches.

Olmesartan is a third-generation high-affinity ARB with a 12- to 15-hour half-life that is prescribed once daily.[1,21] It is available as a dual combination product with hydrochlorothiazide or amlodipine and as a triple combination preparation with both of these agents.[21] No clinical trials demonstrating reductions in cardiovascular morbidity and mortality outcomes have been published.[22] The ongoing 1147 patient Supplemental Benefit of an Angiotensin Receptor Blocker in Hypertensive Patients with Stable Heart Failure Using Olmesartan (SUPPORT) trial is evaluating the efficacy of olmesartan compared with non-ARB antihypertensives in reducing a composite of all-cause mortality, nonfatal acute myocardial infarction, nonfatal stroke, and hospital admissions for heart failure.[23] Results are expected in 2013 to 2014.

Potential mechanisms to explain the association between olmesartan use and increased hospitalizations are not known. A J-curve mechanism resulting from excessive diastolic blood pressure lowering has been proposed to explain increased cardiovascular risk with olmesartan use in placebo-controlled studies.[3,4] Notably, previous studies comparing olmesartan with either placebo or atenolol therapy have reported that olmesartan leads to comparatively favorable improvements in such surrogate cardiovascular end points as vascular remodeling, endothelial dysfunction, inflammatory biomarkers, and atherosclerotic plaque volume.[24–26] In addition, olmesartan has been proposed to possess potential cardiovascular benefits compared with other ARBs because it is an inverse agonist at the angiotensin II type 1 receptor and because it reduces plasma angiotensin II levels.[23,27] Thus, overall, published data support the hypothesis that olmesartan should reduce rather than increase cardiovascular events. It is possible that mechanistic studies to assess potential harm have yet to be performed given that signals for potential harm have only been recently reported.

Similarly, no mechanisms to definitively explain the putative association between olmesartan and sprue-like enteropathy are known. Case reports indicate that symptoms appear months to years after olmesartan initiation.[28,29] Intestinal biopsies have revealed villous atrophy with mucosal inflammation and symptoms improve after drug discontinuation but not a gluten-free diet.[28,29] IgA transglutaminase antibodies are notably absent.[29] A cell-mediated or delayed hypersensitivity reaction, potentially associated with the human leukocyte antigen-DQ cell surface receptor type 2, has been proposed.[29]

Strengths of this study include the availability of a nationally representative, clinically rich data set; a relatively large sample size and long follow-up duration; a comparative effectiveness design in which olmesartan was compared directly against other ARBs; the use of advanced statistical techniques to adjust for potential confounders (including propensity score analysis); and conduction of extensive sensitivity analyses. Limitations include the retrospective, observational nature of the study design, the relatively short follow-up period (median 2.3 years was shorter than ROADMAP [median 3.2] and ORIENT [mean 3.2]), and the inability to adjust for additional potential confounders. The most important missing confounder was blood pressure, and we acknowledge that the observed differences in outcomes could have resulted from differences in blood pressure control. For example, in the overall cohort, subjects with losartan notably had less comorbidity at baseline, and the inability to adjust

Table 3. Subgroup Analyses in High-Risk Subjects Comparing Olmesartan Users With Users of All Other Angiotensin Receptor Blockers

	History of Cardiovascular Disease (n=8755)				CKD (GFR<60 mL/min; n=4575)			
Outcome	Adjusted HR (95% CI)	*P* Value	Time at Risk (Person -Years)	Events, n (%)	Adjusted HR (95% CI)	*P* Value	Time at Risk (Person-Years)	Events, n (%)
All-cause hospitalization or mortality	1.11 (0.99–1.24)	0.08	2008	363 (4)	1.21 (1.04–1.41)	0.02	1131	208 (5)
All-cause mortality	1.09 (0.59–2.03)	0.78	2462	12 (0)	0.88 (0.40–1.97)	0.76	1364	7 (0)
All-cause hospitalization	1.12 (0.99–1.25)	0.06	2008	362 (4)	1.23 (1.05–1.43)	0.009	1131	208 (5)
CV disease–related hospitalization	1.19 (0.98–1.46)	0.09	2335	115 (1)	1.30 (0.96–1.76)	0.09	1322	52 (1)
GI disease–related hospitalization	1.10 (0.87–1.37)	0.46	2348	91 (1)	1.27 (0.94–1.70)	0.12	1303	58 (1)
Noninfective enteritis and colitis-related admissions	1.13 (0.69–1.85)	0.62	2451	7 (0)	1.38 (0.79–2.42)	0.26	1351	9 (0)

CI indicates confidence interval; CV, cardiovascular; CKD, chronic kidney disease; GI, gastrointestinal; GFR, glomerular filtration rate; and HR, hazard regression.

for residual confounding may explain why there was a trend toward a lower hazard for the primary end point in olmesartan users in the overall group, yet risk was increased in the high-risk subgroups. Thus, it is important to emphasize that this type of study design provides associative and not causal evidence. In addition, all included subjects were middle aged Americans with commercial health insurance, which should be borne in mind when generalizing the results beyond this population. In particular, despite having cardiovascular risk factors or pre-existing disease, our study population had a crude death rate of only 392 per 100 000, which is lower than the 2010 crude death rate for all US adults aged 50 to 54 years (491.7 per 100 000)[30] and indicates that the study population was relatively healthy and well treated. Finally, we did not have information on cause-specific mortality and could not directly evaluate the association between olmesartan use and cardiovascular mortality.

Perspectives

Olmesartan is a commonly prescribed antihypertensive drug, and recent evidence linking this agent to an increased risk of cardiovascular mortality and sprue-like enteropathy mandates the need for further study. Analyses of large-scale clinical registry data serve as a useful and important complement to randomized controlled trial data in terms of assessing drug-related harm. In the present analysis, although there was a suggestion that patients with CKD may be at higher risk of all-cause mortality or hospitalization, findings that would be consistent with the results of the ROADMAP study,[3,4] our findings are not sufficiently robust or consistent to support the conclusion that olmesartan increases risk in patients with diabetes mellitus. About the subgroup of patients with CKD, given the results of ROADMAP and ORIENT and given our findings, we recommend that olmesartan use be used with caution in this patient population until further mechanistic, epidemiological, and interventional studies to clarify the effect of this drug on clinically important end points have been performed. We also recommend that further postmarketing surveillance of this agent be performed to assess risk in a more comprehensive fashion in different study samples and populations. This should take the form of additional analyses of clinical registries as well as a meta-analysis of individual patient-level data from previously published and soon-to-be-published randomized controlled trials.

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R. Padwal originated the study idea and all authors contributed to the conception and design, the analysis, and interpretation of data. D.T. Eurich and M. Lin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. R. Padwal and D.T. Eurich wrote the initial manuscript draft, all authors revised it critically for important intellectual content, and all authors provided final approval of the version to be published. We would also like to acknowledge Betsey Jackson at Health Data Services Corporation (www.hdscorp.biz), PO Box 53, Carlisle, MA 01741 for providing independent database acquisition services.

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Novelty and Significance

What Is New?

- Olmesartan has been linked to an increased risk of cardiovascular mortality in patients with diabetes mellitus.
- We conducted a retrospective analysis of >45 000 subjects using a nationwide US-integrated insurance and laboratory claims database.
- In a risk-adjusted analysis that included propensity scores, no increased risk of all-cause mortality or hospitalization was found in our overall cohort although risk may be increased in patients with chronic kidney disease.

What Is Relevant?

- Olmesartan is commonly prescribed.
- To our knowledge, this is the first large comparative effectiveness study involving olmesartan in patients with diabetes mellitus.

Summary

We found no robust signal for harm and no compelling reason to avoid the drug except, perhaps, in patients with chronic kidney disease. Further study is required, especially in diabetics with chronic kidney disease.

Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes: Retrospective Cohort Study

Online Supplement

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Supplementary Methods

Dose-Response Sensitivity Analysis

A dose-response sensitivity analysis was also performed in which we used a standard (i.e., non-time dependent) Cox model to examine the association between tertiles of the average daily dose prescribed (low/medium/high) and the primary outcome in olmesartan users only. Subjects with the lowest level of exposure served as the reference group. Model covariates were identical to those used in the primary analysis except the propensity score adjusted for the propensity to receive a medium or high dose of olmesartan (compared to a low dose). To account for changes in dose over time, average daily dose was calculated by dividing the total dose prescribed over the follow-up period by the total drug exposure time. To calculate follow-up time, each subject was considered exposed to the drug until an event occurred (death or hospitalization), their insurance coverage was terminated or they discontinued therapy. If insurance coverage was terminated or treatment was discontinued, subjects were censored, with a censoring date of 60 days after the date on which their last prescription had ended. We also performed the same dose-response analysis for losartan and valsartan as a further sensitivity analysis. We did this to determine whether or not findings of the olmesartan dose-response analysis were similar for another ARB or specific to olmesartan alone.

Individual ARB Analysis

As a further sensitivity analysis, we performed an individual ARB analysis by dividing the primary cohort into separate ARB groups [olmesartan, losartan, valsartan, telmisartan and all others (candesartan, eprosartan and irbesartan)] and repeated the primary endpoint analysis (models adjusted as described above) to determine if olmesartan was associated with the highest risk of all-cause hospital admission or death. Olmesartan was used as the base comparator in this analysis, which was performed in the overall cohort and in the subgroups with pre-existing cardiovascular disease and chronic kidney disease. Subjects switching ARB agents were censored at the time the switch occurred.

Table S1. Sensitivity analysis examining the dose-response relationship within users of olmesartan, losartan and valsartan.

Group	Dose Tertiles	Medium Dose vs. Low Dose aHR (95% CI)	High Dose vs. Low Dose aHR (95% CI)
Olmesartan (n=10370)			
Overall cohort	Low: <18.7 mg Medium: 18.7-29.8 mg High: ≥29.9 mg	1.18 (1.04-1.34)	1.20 (1.05-1.37)
Cardiovascular disease	Low: <18.6 mg Medium: 18.6-30.1 mg High: ≥30.2 mg	1.62 (1.21-2.17)	1.40 (1.03-1.90)
Chronic kidney disease	Low: <19.9 mg Medium: 19.9-32.3 mg High: ≥32.4 mg	0.77 (0.51-1.14)	1.44 (0.99-2.10)
Losartan Sensitivity Analysis (n=8656)			
Overall cohort	Low: <37.4 mg Medium: 37.4-60.8 mg High: ≥60.8 mg	1.06 (0.96-1.19)	0.86 (0.77-0.97)

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